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1 Refining the accuracy of validated target 2 identification through coding variant fine- 3 mapping in type 2 diabetes

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We aggregated coding variant data for 81,412 type 2 diabetes cases and 370,832 controls of diverse ancestry, identifying 40 coding variant association signals ($p < 2.2 \times 10^{-7}$): of these, 16 map outside known risk loci. We make two important observations. First, only five of these signals are driven by low-frequency variants: even for these, effect sizes are modest (odds ratio ≤ 1.29). Second, when we used large-scale genome-wide association data to fine-map the associated variants in their regional context, accounting for the global enrichment of complex trait associations in coding sequence, compelling evidence for coding variant causality was obtained for only 16 signals. At 13 others, the associated coding variants clearly represent “false leads” with potential to generate erroneous mechanistic inference. Coding variant associations offer a direct route to biological insight for complex diseases and identification of validated therapeutic targets: however, appropriate mechanistic inference requires careful specification of their causal contribution to disease predisposition.

Genome-wide association studies (GWAS) have identified thousands of association signals influencing multifactorial traits such as type 2 diabetes (T2D) and obesity¹⁻⁷. Most of these associations involve common variants that map to non-coding sequence, and identification of their cognate effector transcripts has proved challenging. Identification of coding variants causally implicated in trait predisposition offers a more direct route from association signal to biological inference.

The exome occupies 1.5% of overall genome sequence, but for many common diseases, coding variants make a disproportionate contribution to trait heritability^{8,9}. This enrichment indicates that coding variant association signals have an enhanced probability of being causal when compared to those involving an otherwise equivalent non-coding variant. This does not, however, guarantee that all coding variant associations are causal. Alleles driving common-variant (minor allele frequency [MAF] $\geq 5\%$) GWAS signals typically reside on extended risk haplotypes that, owing to linkage disequilibrium (LD), incorporate many common variants^{10,11}. Consequently, the presence of a coding allele on the risk haplotype does not constitute sufficient evidence that it represents the causal variant at the locus, or that the gene within which it lies is mediating the association signal. Since much coding variant discovery has proceeded through exome-specific analyses (either exome-array genotyping or exome sequencing), researchers have often been poorly-placed to position

coding variant associations in the context of regional genetic variation. It is unclear how often this may have led to incorrect assumptions regarding their causal role.

In our recent study of T2D predisposition¹², we surveyed the exomes of 34,809 T2D cases and 57,985 controls, of predominantly European descent, and identified 13 distinct coding variant associations reaching genome-wide significance. Twelve of these associations involved common variants, but the data hinted at a substantial pool of lower-frequency coding variants of moderate impact, potentially amenable to detection in larger samples. We also reported that, whilst many of these signals fell within common variant loci previously identified by GWAS, it was far from trivial to determine, using available data, whether those coding variants were causal or ‘hitchhiking’ on risk haplotypes.

Here, we report analyses that address these two issues. First, we extend the scope of our exome-array genotyping to include data from 81,412 T2D cases and 370,832 controls of diverse ancestry, substantially increasing power to detect coding variant associations across the allele-frequency spectrum. Second, to understand the extent to which identification of coding variant associations provides a reliable guide to causal mechanisms, we undertake high-resolution fine-mapping of identified coding variant association signals in 50,160 T2D cases and 465,272 controls of European ancestry with genome-wide genotyping data.

RESULTS

Discovery study overview. First, we set out to discover coding variant association signals by aggregating T2D association summary statistics in up to 452,244 individuals (effective sample size 228,825) across five ancestry groups, performing both European-specific (EUR) and trans-ethnic (TE) meta-analyses (**Supplementary Tables 1 and 2**). Analysis was restricted to the 247,470 variants represented on the exome-array. Genotypes were assembled from: (a) 58,425 cases and 188,032 controls genotyped with the exome-array; (b) 14,608 cases and 174,322 controls from UK Biobank and GERA (Resource for Genetic Epidemiology on Adult Health and Aging) genotyped with GWAS arrays enriched for exome content and/or coverage of low-frequency variation across ethnic groups^{13,14}; and (c) 8,379 cases and 8,478 controls with whole-exome sequence from GoT2D/T2D-GENES¹² and SIGMA¹⁵ studies. Overall, this represented a 3-fold increase in effective sample size over our previous study of T2D predisposition within coding sequence¹². To deconvolute the impact

of obesity on T2D-associated variants, association analyses were conducted with and without body mass index (BMI) adjustment.

We considered $p < 2.2 \times 10^{-7}$ as significant for protein truncating variants (PTVs) and moderate impact coding variants (including missense, in-frame indel and splice region variants) based on a weighted Bonferroni correction that accounts for the observed enrichment in complex trait association signals across sequence annotation¹⁶. This threshold matches those obtained through other approaches such as simple Bonferroni correction for the number of coding variants on the exome-array (**Methods**). Compared to our previous study¹², the expanded sample size substantially increased power to detect association for common variants of modest effect (e.g. from 14.4% to 97.9% for a variant with 20% MAF and odds ratio [OR]=1.05) and lower-frequency variants with larger effects (e.g. from 11.8% to 97.5% for a variant with 1% MAF and OR=1.20) assuming homogenous allelic effects across ancestry groups (**Methods**).

Insights into coding variant association signals underlying T2D susceptibility. We detected significant associations at 69 coding variants under an additive genetic model (either in BMI unadjusted or adjusted analysis), mapping to 38 loci (**Supplementary Fig. 1, Supplementary Table 3**). We observed minimal evidence of heterogeneity in allelic OR between ancestry groups (**Supplementary Table 3**), and no compelling evidence for non-additive allelic effects (**Supplementary Fig. 2, Supplementary Table 4**). Reciprocal conditional analyses (**Methods**) indicated that the 69 coding variants represented 40 distinct association signals (conditional $p < 2.2 \times 10^{-7}$) across the 38 loci, with two distinct signals each at *HNF1A* and *RREB1* (**Supplementary Table 5**). These 40 signals included the 13 associations reported in our earlier publication¹², each featuring more significant associations in this expanded meta-analysis (**Supplementary Table 6**). Twenty-five of the 40 signals were significant in both EUR and TE analyses. Of the other 15, three (*PLCB3*, *C17orf58*, and *ZHX3*) were significant in EUR, and all reached $p_{TE} < 6.8 \times 10^{-6}$ in the TE analysis: for *PLCB3* and *ZHX3*, risk allele frequencies were substantially lower outside European descent populations. Twelve loci (**Supplementary Table 3**) were significant in TE alone, but for these (except *PAX4* which is East Asian specific), the evidence for association was proportionate in the smaller EUR component ($p_{EUR} < 8.4 \times 10^{-5}$).

Sixteen of the 40 distinct association signals mapped outside regions previously implicated in T2D susceptibility (Methods, **Table 1**). These included missense variant signals in *POC5* (p.His36Arg, rs2307111, $p_{TE}=1.6 \times 10^{-15}$), *PNPLA3* (p.Ile148Met, rs738409, p_{TE} BMI-adjusted= 2.8×10^{-11}), and *ZZEF1* (p.Ile2014Val, rs781831, $p_{TE}=8.3 \times 10^{-11}$).

In addition to the 69 coding variant signals, we detected significant ($p < 5 \times 10^{-8}$) and novel T2D-associations for 20 non-coding variants (at 15 loci) that were also assayed on the exome-array (**Supplementary Table 7**). Three of these (*POC5*, *LPL*, and *BPTF*) overlap with novel coding signals reported here.

Contribution of low-frequency and rare coding variation to T2D susceptibility. Despite increased power and good coverage of low-frequency variants on the exome-array¹², 35 of the 40 distinct coding variant association signals were common, with modest effects (allelic ORs 1.02-1.36) (**Supplementary Fig. 3, Supplementary Table 3**). The five signals attributable to lower-frequency variants were also of modest effect (allelic ORs 1.09-1.29) (**Supplementary Fig. 3**). Two of the lower-frequency variant signals were novel, and in both, the minor allele was protective against T2D: *FAM63A* p.Tyr95Asn (rs140386498, MAF=1.2%, OR= 0.82 [0.77-0.88], $p_{EUR}=5.8 \times 10^{-8}$) and *ANKH* p.Arg187Gln (rs146886108, MAF=0.4%, OR=0.78 [0.69-0.87], $p_{EUR}=2.0 \times 10^{-7}$). Both variants were very rare or monomorphic in non-European descent individuals.

In Fuchsberger et al.¹², we highlighted a set of 100 low-frequency coding variants with allelic ORs between 1.10 and 2.66, which despite relatively large estimates for liability-scale variance explained, had not reached significance. In this expanded analysis, only five of these variants, including the two novel associations at *FAM63A* p.Tyr95Asn and *ANKH* p.Arg187Gln, attained significance. More precise effect-size estimation in the larger sample size indicates that OR estimates in the earlier study were subject to a substantial upwards bias (**Supplementary Fig. 3**).

To detect additional rare variant association signals, we performed gene-based analyses (burden and SKAT¹⁷) using previously-defined “strict” and “broad” masks, filtered for annotation and MAF^{12,18} (**Methods**). We identified gene-based associations with T2D susceptibility ($p < 2.5 \times 10^{-6}$, Bonferroni correction for 20,000 genes) for *FAM63A* (10 variants, combined MAF=1.9%, $p_{EUR}=3.1 \times 10^{-9}$) and *PAM* (17 variants, combined MAF=4.7%, $p_{TE}=8.2 \times 10^{-9}$). On conditional analysis (**Supplementary Table 8**), the gene-based signal at

FAM63A was entirely attributable to the low-frequency p.Tyr95Asn allele described earlier (conditional $p=0.26_{EUR}$). The gene-based signal for *PAM* was also driven by a single low-frequency variant (p.Asp563Gly; conditional $p_{TE}=0.15$). A second, previously-described, low-frequency variant, *PAM* p.Ser539Trp¹⁹, is not represented on the exome-array, and did not contribute to these analyses.

Fine-mapping of coding variant association signals with T2D susceptibility. These analyses identified 40 distinct coding variant associations with T2D, but this information is not sufficient to determine that these variants are causal for disease. To assess the role of these coding variants given regional genetic variation, we fine-mapped these association signals using a meta-analysis of 50,160 T2D cases and 465,272 controls (European-descent only; partially overlapping with the discovery samples), which we aggregated from 24 GWAS. Each component GWAS was imputed using appropriate high-density reference panels (for most, the Haplotype Reference Consortium²⁰; **Methods, Supplementary Table 9**). Before fine-mapping, distinct association signals were delineated using approximate conditional analyses (**Methods, Supplementary Table 5**). We included 37 of the 40 identified coding variants in this fine-mapping analysis, excluding three (those at the *MHC*, *PAX4*, and *ZHX3*) that were, for various reasons (see **Methods**), not amenable to fine-mapping in the GWAS data.

For each of these 37 signals, we first constructed “functionally-unweighted” credible variant sets, which collectively account for 99% of the posterior probability of association (PPA), based exclusively on the meta-analysis summary statistics²¹ (**Methods, Supplementary Table 10**). For each signal, we calculated the proportion of PPA attributable to coding variants (missense, in-frame indel, and splice region variants; **Figure 1, Supplementary Fig. 4 and 5**). There were only two signals at which coding variants accounted for $\geq 80\%$ of PPA: *HNF4A* p.Thr139Ile (rs1800961, PPA>0.999) and *RREB1* p.Asp1171Asn (rs9379084, PPA=0.920). However, at other signals, including those for *GCKR* p.Pro446Leu and *SLC30A8* p.Arg276Trp, for which robust empirical evidence has established a causal role^{22,23}, genetic support for coding variant causation was weak. This is because coding variants were typically in high LD ($r^2>0.9$) with large numbers of non-coding variants, such that the PPA was distributed across many sites with broadly equivalent evidence for association.

These functionally-unweighted sets are based on genetic fine-mapping data alone, and do not account for the disproportionate representation of coding variants amongst GWAS associations for complex traits^{8,9}. To accommodate this information, we extended the fine-mapping analyses by incorporating an “annotation-informed prior” model of causality. We derived priors from estimates of the enrichment of association signals by sequence annotation from analyses conducted by deCODE across 96 quantitative and 123 binary phenotypes¹⁶ (**Methods**). This model “boosts” the prior, and hence the posterior probabilities (we use ‘ aiPPA ’ to denote annotation-informed PPAs) of coding variants. It also takes account (in a tissue-non-specific manner) of the GWAS enrichment of variants within enhancer elements (as assayed through DNase I hypersensitivity) when compared to non-coding variants mapping elsewhere. The annotation-informed model generated smaller 99% credible sets across most signals, corresponding to fine-mapping at higher resolution (**Supplementary Table 10**). As expected, the contribution of coding variants was increased under the annotation-informed model. At these 37 association signals, we distinguished three broad patterns of causal relationships between coding variants and T2D risk.

Group 1: T2D association signal is driven by coding variants. At 16 of the 37 distinct signals, coding variation accounted for >80% of the aiPPA (**Fig. 1, Table 2, Supplementary Table 10**). This was attributable to a single coding variant at 12 signals and multiple coding variants at four. Reassuringly, group 1 signals confirmed coding variant causation for several loci (*GCKR*, *PAM*, *SLC30A8*, *KCNJ11-ABCC8*) at which functional studies have established strong mechanistic links to T2D pathogenesis (**Table 2**). T2D association signals at the 12 remaining signals (**Fig. 1, Supplementary Table 10**) had not previously been shown to be driven by coding variation, but our fine-mapping analyses pointed to causal coding variants with high aiPPA values: these included *HNF4A*, *RREB1* (p. Asp1171Asn), *ANKH*, *WSCD2*, *POC5*, *TM6SF2*, *HNF1A* (p. Ala146Val; p. Ile75Leu), *GIPR*, *LPL*, *PLCB3*, and *PNPLA3* (**Table 2**). At several of these, independent evidence corroborates the causal role of the genes harbouring the associated coding variants. For example, rare coding mutations at *HNF1A* and *HNF4A* are causal for monogenic, early-onset forms of diabetes²⁴; and at *TM6SF2* and *PNPLA3*, the associated coding variants are implicated in the development of non-alcoholic fatty liver disease (NAFLD)^{25,26}.

The use of priors to capture the enrichment of coding variants seems a reasonable model, genome-wide. However, at any given locus, strong priors (especially for PTVs) might elevate to apparent causality, variants that would have been excluded from a causal role on the basis of genetic fine-mapping alone. Comparison of the annotation-informed and functionally-unweighted credible sets for group 1 signals indicated that this scenario was unlikely. For 11 of the 16 (*GCKR*, *PAM*, *KCNJ11-ABCC8*, *HNF4A*, *RREB1* [p.Asp1171Asn], *ANKH*, *POC5*, *TM6SF2*, *HNF1A* [p.Ala146Val], *PLCB3*, *PNPLA3*), the coding variant had the highest PPA in the fine-mapping analysis (**Table 2**) even under the functionally-unweighted model. At *SLC30A8*, *WSCD2*, and *GIPR*, the coding variants had similar PPAs to the lead non-coding SNPs under the functionally-unweighted prior (**Table 2**). At these 14 signals therefore, coding variants have either greater or equivalent PPA to the best flanking non-coding SNPs under the functionally-unweighted model, but receive a boost in PPA after incorporating the annotation weights.

The situation is less clear at *LPL*. Here, fine-mapping resolution is poor under the functionally-unweighted prior, and the coding variant sits on an extended haplotype in strong LD with non-coding variants, some with higher PPA, such as rs74855321 (PPA=0.048) (compared to *LPL* p.Ser474* [rs328, PPA=0.023]). However, *LPL* p.Ser474* is annotated as a PTV, and benefits from a substantially-increased prior that boosts its annotation-informed ranking (**Table 2**). Ultimately, decisions regarding the causal role of any such variant must rest on the amalgamation of evidence from diverse sources including detailed functional evaluation of the coding variants, and of other variants with which they are in LD.

Group 2: T2D association signals are not attributable to coding variants. At 13 of the 37 distinct signals, coding variation accounted for <20% of the PPA, even after applying the annotation-informed prior model. These signals are likely to be driven by local non-coding variation and mediated through regulatory mechanisms. Five of these signals (*TPCN2*, *MLX*, *ZZEF1*, *C17orf58*, and *CEP68*) represent novel T2D-association signals identified in the exome-focused analysis. Given the exome-array discoveries, it would have been natural to consider the named genes at these, and other loci in this group, as candidates for mediation of their respective association signals. However, the fine-mapping analyses indicate that these coding variants do not provide useful mechanistic inference given low a_i PPA (**Fig. 1**, **Table 2**).

The coding variant association at the *CENTD2* (*ARAP1*) locus is a case-in-point. The association with the p.Gln802Glu variant in *ARAP1* (rs56200889, $p_{TE}=4.8 \times 10^{-8}$ but $aiPPA < 0.001$) is seen in the fine-mapping analysis to be secondary to a substantially stronger non-coding association signal involving a cluster of variants including rs11603334 ($p_{TE}=9.5 \times 10^{-18}$, $aiPPA=0.0692$) and rs1552224 ($p_{TE}=2.5 \times 10^{-17}$, $aiPPA=0.0941$). The identity of the effector transcript at this locus has been the subject of detailed investigation, and some early studies used islet expression data to promote *ARAP1*²⁷. However, a more recent study integrating human islet genomics and murine gene knockout data establishes *STARD10* as the gene mediating the GWAS signal, consistent with the reassignment of the *ARAP1* coding variant association as irrelevant to causal inference²⁸.

Whilst, at these loci, the coding variant associations represent “false leads”, this does not necessarily exclude the genes concerned from a causal role. At *WFS1* for example, coding variants too rare to be visible to the array-based analyses we performed, and statistically independent of the common p.Val333Ile variant we detected, cause an early-onset form of diabetes that renders *WFS1* the strongest local candidate for T2D predisposition.

Group 3: Fine-mapping data consistent with partial role for coding variants. At eight of the 37 distinct signals, the $aiPPA$ attributable to coding variation lay between 20% and 80%. At these signals, the evidence is consistent with “partial” contributions from coding variants, although the precise inference is likely to be locus-specific, dependent on subtle variations in LD, imputation accuracy, and the extent to which global priors accurately represent the functional impact of the specific variants concerned.

This group includes *PPARG* for which independent evidence corroborates the causal role of this specific effector transcript with respect to T2D-risk. *PPARG* encodes the target of antidiabetic thiazolidinedione drugs and harbours very rare coding variants causal for lipodystrophy and insulin resistance, conditions highly-relevant to T2D. The common variant association signal at this locus has generally been attributed to the p.Pro12Ala coding variant (rs1801282) although empirical evidence that this variant influences *PPARG* function is scant²⁹⁻³¹. In the functionally-unweighted analysis, p.Pro12Ala had an unimpressive PPA (0.0238); after including annotation-informed priors, the same variant emerged with the highest $aiPPA$ (0.410), although the 99% credible set included 19 non-coding variants,

spanning 67kb (**Supplementary Table 10**). These credible set variants included rs4684847 ($\text{aiPPA}=0.0089$), at which the T2D-associated allele has been reported to impact *PPARG2* expression and insulin sensitivity by altering binding of the homeobox transcription factor PRRX1³². These data are consistent with a model whereby regulatory variants contribute to altered PPARG activity in combination with, or potentially to the exclusion of, p.Pro12Ala. Future improvements in functional annotation for regulatory variants (gathered from relevant tissues and cell types) should provide increasingly granular priors that allow fine-tuned assignment of causality at loci such as this.

Functional impact of coding alleles. In other contexts, the functional impact of coding alleles is correlated with: (i) variant-specific features, including measures of conservation and predicted impact on protein structure; and (ii) gene-specific features such as extreme selective constraints as quantified by the intolerance to functional variation³³. To determine whether similar measures could capture information pertinent to T2D causation, we compared coding variants falling into the different fine-mapping groups for a variety of measures including MAF, Combined Annotation Dependent Depletion (CADD) score³⁴, and loss-of-function (LoF)-intolerance metric, pLI³³ (**Methods, Fig. 2**). Variants from group 1 had significantly higher CADD-scores than those in group 2 (Kolmogorov-Smirnov $p=0.0031$). Except for the variants at *KCNJ11-ABCC8* and *GCKR*, all group 1 coding variants considered likely to be driving T2D association signals had CADD-score ≥ 20 . On this basis, we predict that the East-Asian specific coding variant at *PAX4*, for which the fine-mapping data were not informative, is also likely causal for T2D.

T2D loci and physiological classification. The development of T2D involves dysfunction of multiple mechanisms. Systematic analysis of the physiological effects of known T2D-risk alleles has improved understanding of the mechanisms through which they exert their primary impact on disease risk³⁵. We obtained association summary statistics for diverse metabolic traits (and other outcomes) for 94 T2D-associated index variants. These 94 were restricted to sites represented on the exome-array and included the 40 coding signals plus 54 distinct non-coding signals (12 novel and 42 previously-reported non-coding GWAS lead SNPs). We applied clustering techniques (**Methods**) to generate multi-trait association patterns, allocating 71 of the 94 loci to one of three main physiological categories

(**Supplementary Figs. 6, Supplementary Table 11**). The first category, comprising nine T2D-risk loci with strong BMI and dyslipidemia associations, included three of the novel coding signals: *PNPLA3*, *POC5* and *BPTF*. The T2D associations at both *POC5* and *BPTF* were substantially attenuated (>2 -fold decrease in $-\log_{10}p$) after adjusting for BMI (**Table 1, Supplementary Table 3, Supplementary Fig. 7**), indicating that their impact on T2D-risk is likely mediated by a primary effect on adiposity. *PNPLA3* and *POC5* are established NAFLD²⁵ and BMI⁶ loci, respectively. The second category featured 39 loci at which multi-trait profiles indicated a primary effect on insulin secretion. This set included four of the novel coding variant signals (*ANKH*, *ZZEF1*, *TTLL6*, *ZHX3*). The third category encompassed 23 loci with primary effects on insulin action, including signals at the *KIF9*, *PLCB3*, *CEP68*, *TPCN2*, *FAM63A*, and *PIM3* loci. For most variants in this category, the T2D-risk allele was associated with lower BMI, and T2D association signals were more pronounced after adjustment for BMI. At a subset of these loci, including *KIF9* and *PLCB3*, T2D-risk alleles were associated with higher waist-hip ratio and lower body fat percentage, indicating that the mechanism of action likely reflects limitations in storage capacity of peripheral adipose tissue³⁶.

DISCUSSION

The present study adds to mounting evidence constraining the contribution of lower-frequency variants to T2D-risk. Although the exome-array interrogates only a subset of the universe of coding variants, it captures the majority of low-frequency coding variants in European populations. The substantial increase in sample size in the present study over our previous effort¹² (effective sample sizes of 228,825 and 82,758, respectively), provides more robust evaluation of the effect size distribution in this low-frequency variant range, and indicates that previous analyses are likely, if anything, to have overestimated the contribution of low-frequency variants to T2D-risk.

The present study is less informative regarding rare variants. These are sparsely captured on the exome-array. In addition, the combination of greater regional diversity in rare allele distribution and the enormous sample sizes required to detect rare variant associations (likely to require meta-analysis of data from diverse populations) acts against their identification. Our complementary genome and exome sequence analyses have thus far failed to register strong evidence for a substantial rare variant component to T2D-risk¹².

It is therefore highly unlikely that rare variants missed in our analyses are causal for any of the common or low-frequency variant associations we have detected and fine-mapped. On the other hand, it is probable that rare coding alleles, with associations that are distinct from the common variant signals we have examined and detected only through sequence based analyses, will provide additional clues to the most likely effector transcripts at some of these signals (*WFS1* provides one such example).

Once a coding variant association is detected, it is natural to assume a causal connection between that variant, the gene in which it sits, and the phenotype of interest. Whilst such assignments may be robust for many rare protein-truncating alleles, we demonstrate that this implicit assumption is often inaccurate, particularly for associations attributable to common, missense variants. A third of the coding variant associations we detected were, when assessed in the context of regional LD, highly unlikely to be causal. At these loci, the genes within which they reside are consequently deprived of their implied connection to disease risk, and attention redirected towards nearby non-coding variants and their impact on regional gene expression. As a group, coding variants we assign as causal are predicted to have a more deleterious impact on gene function than those that we exonerate, but, as in other settings, coding annotation methods lack both sensitivity and specificity. It is worth emphasising that empirical evidence that the associated coding allele is “functional” (i.e. can be shown to influence cognate gene function in some experimental assay) provides limited reassurance that the coding variant is responsible for the T2D association, unless that specific perturbation of gene function can itself be plausibly linked to the disease phenotype.

Our fine-mapping analyses make use of the observation that coding variants are globally enriched across GWAS signals^{8,9,16} with greater prior probability of causality assigned to those with more severe impact on biological function. We assigned diminished priors to non-coding variants, with lowest support for those mapping outside of DNase I hypersensitive sites. The extent to which our findings corroborate previous assignments of causality (often substantiated by detailed, disease-appropriate functional assessment and other orthogonal evidence) suggests that even these sparse annotations provide valuable information to guide target validation. Nevertheless, there are inevitable limits to the extrapolation of these ‘broad-brush’ genome-wide enrichments to individual loci: improvements in functional annotation for both coding and regulatory variants, particularly

when gathered from trait-relevant tissues and cell types, should provide more granular, trait-specific priors to fine-tune assignment of causality within associated regions. These will motivate target validation efforts that benefit from synthesis of both coding and regulatory mechanisms of gene perturbation. It also needs to be acknowledged that, without whole genome sequencing data on sample sizes comparable to those we have examined here, imperfections arising from the imputation may confound fine-mapping precision at some loci, and that robust inference will inevitably depend on integration of diverse sources of genetic, genomic and functional data.

The term “smoking gun” has often been used to describe the potential of functional coding variants to provide causal inference with respect to pathogenetic mechanisms³⁷. This study provides a timely reminder that, even when a suspect with a smoking gun is found at the scene of a crime, it should not be assumed that they fired the fatal bullet.

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819 **DISCLOSURES**

820 Jose C Florez has received consulting honoraria from Merck and from Boehringer-Ingelheim.
821 Daniel I Chasman received funding for exome chip genotyping in the WGHS from Amgen.
822 Oscar H Franco works in ErasmusAGE, a center for aging research across the life course
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824 Ltd.), Metagenics Inc., and AXA had no role in the design and conduct of the study;
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827 Wellness, Inc., and advisor for Cellink for work unrelated to the present project. Bruce M

828 Psaty serves on the DSMB for a clinical trial funded by the manufacturer (Zoll LifeCor) and
829 on the Steering Committee of the Yale Open Data Access Project funded by Johnson &
830 Johnson. Inês Barroso and spouse own stock in GlaxoSmithKline and Incyte Corporation.
831 Timothy Frayling has consulted for Boeringer IngelHeim and Sanofi on the genetics of
832 diabetes. Danish Saleheen has received support from Pfizer, Regeneron, Genentech and Eli
833 Lilly. Mark I McCarthy has served on advisory panels for NovoNordisk and Pfizer, and
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FIGURE LEGENDS

Figure 1 | Posterior probabilities for coding variants across loci with annotation-informed

priors. Fine-mapping of 37 distinct association signals was performed using European ancestry GWAS meta-analysis including 50,160 T2D cases and 465,272 controls. For each signal, we constructed a credible set of variants accounting for 99% of the posterior probability of driving the association, incorporating an “annotation informed” prior model of causality which “boosts” the posterior probability of driving the association signal that is attributed to coding variants. Each bar represents a signal with the total probability attributed to the coding variants within the 99% credible set plotted on the y-axis. When the probability (bar) is split across multiple coding variants (at least 0.05 probability attributed to a variant) at a particular locus, these are indicated by blue, pink, yellow, and green colours. The combined probability of the remaining coding variants is highlighted in grey. *RREB1(a): RREB1 p. Asp1171Asn; RREB1(b): RREB1 p.Ser1499Tyr; HNF1A(a): HNF1A p.Ala146Val; HNF1A(b): HNF1A p.Ile75Leu; PPIP5K2† : PPIP5K2 p.Ser1207Gly; MTMR3†: MTMR3 p.Asn960Ser; IL17REL†: IL17REL p.Gly70Arg; NBEAL2†: NBEAL2 p.Arg511Gly, KIF9†: KIF9 p.Arg638Trp.*

Figure 2 | Plot of measures of variant-specific and gene-specific features of distinct coding

signals to assess the functional impact of coding alleles. Each point represents a coding variant with the minor allele frequency plotted on the x-axis and the Combined Annotation Dependent Depletion score (CADD-score) plotted on the y-axis. Size of each point varies with the measure of intolerance of the gene to loss of function variants (pLI) and the colour represents the fine-mapping group each variant is assigned to. Group 1: signal is driven by coding variant. Group 2: signal attributable to non-coding variants. Group 3: consistent with partial role for coding variants. Group 4: Unclassified category; includes *PAX4*, *ZHX3*, and signal at *TCF19* within the MHC region where we did not perform fine-mapping. Inset: plot shows the distribution of CADD-score between different groups. The plot is a combination of violin plots and box plots; width of each violin indicates frequency at the corresponding CADD-score and box plots show the median and the 25% and 75% quantiles. *P* value indicates significance from two-sample Kolmogorov-Smirnov test.

958 **Table 1 | Summary of discovery and fine-mapping analyses of the 40 index coding variants associated with T2D ($p < 2.2 \times 10^{-7}$).**

Discovery meta-analysis using exome-array component: 81,412 T2D cases and 370,832 controls from diverse ancestries															Fine-mapping meta-analysis using GWAS: 50,160 T2D cases and 465,272 controls from European ancestry					
Locus	Index variant	rs ID	Chr	Pos	Alleles	RAF	BMI unadjusted				BMI adjusted				RAF	OR	L95	U95	p-value	Group
					R/O		OR	L95	U95	p-value	OR	L95	U95	p-value						
Previously reported T2D associated loci																				
MACF1	MACF1 p.Met1424Val	rs2296172	1	39,835,817	G/A	0.193	1.06	1.05	1.08	6.7x10 ⁻¹⁶	1.04	1.03	1.06	5.9x10 ⁻⁸	0.22	1.08	1.06	1.1	1.6x10 ⁻¹⁵	3
GCKR	GCKR p.Pro446Leu	rs1260326	2	27,730,940	C/T	0.630	1.06	1.05	1.08	5.3x10 ⁻²⁵	1.06	1.04	1.07	3.2x10 ⁻¹⁸	0.607	1.05	1.04	1.07	9.1x10 ⁻¹⁰	1
THADA	THADA p.Cys845Tyr	rs35720761	2	43,519,977	C/T	0.895	1.08	1.05	1.1	4.6x10 ⁻¹⁵	1.07	1.05	1.10	8.3x10 ⁻¹⁶	0.881	1.1	1.07	1.12	3.4x10 ⁻¹²	2
GRB14	COBLL1 p.Asn901Asp	rs7607980	2	165,551,201	T/C	0.879	1.08	1.06	1.11	8.6x10 ⁻²⁰	1.09	1.07	1.12	5.0x10 ⁻²³	0.871	1.08	1.06	1.11	3.6x10 ⁻¹⁰	2
PPARG	PPARG p.Pro12Ala	rs1801282	3	12,393,125	C/G	0.887	1.09	1.07	1.11	1.4x10 ⁻¹⁷	1.10	1.07	1.12	2.7x10 ⁻¹⁹	0.876	1.12	1.09	1.14	3.7x10 ⁻¹⁷	3
IGF2BP2	SEN2 p.Thr291Lys	rs6762208	3	185,331,165	A/C	0.367	1.03	1.01	1.04	1.6x10 ⁻⁶	1.03	1.02	1.05	3.0x10 ⁻⁸	0.339	1.02	1.01	1.04	0.01	2
WFS1	WFS1 p.Val333Ile	rs1801212	4	6,302,519	A/G	0.748	1.07	1.06	1.09	1.1x10 ⁻²⁴	1.07	1.05	1.08	7.1x10 ⁻²¹	0.703	1.07	1.05	1.09	4.1x10 ⁻¹³	2
PAM-PP1P5K2	PAM p.Asp336Gly	rs35658696	5	102,338,811	G/A	0.045	1.13	1.10	1.17	1.2x10 ⁻¹⁶	1.13	1.09	1.17	7.4x10 ⁻¹⁵	0.051	1.17	1.13	1.22	2.5x10 ⁻¹⁷	1
RREB1	RREB1 p.Asp1171Asn	rs9379084	6	7,231,843	G/A	0.884	1.08	1.06	1.11	1.1x10 ⁻¹³	1.10	1.07	1.13	1.5x10 ⁻¹⁷	0.888	1.09	1.06	1.12	1.1x10 ⁻⁹	1
	RREB1 p.Ser1499Tyr	rs35742417	6	7,247,344	C/A	0.836	1.04	1.03	1.06	5.5x10 ⁻⁸	1.04	1.02	1.06	2.2x10 ⁻⁷	0.817	1.04	1.02	1.07	0.00012	2
MHC	TCF19 p.Met131Val	rs2073721	6	31,129,616	G/A	0.749	1.04	1.02	1.05	1.6x10 ⁻¹⁰	1.04	1.02	1.05	2.3x10 ⁻⁹	N/A	N/A	N/A	N/A	N/A	N/A
PAX4	PAX4 p.Arg190His	rs2233580	7	127,253,550	T/C	0.029	1.36	1.25	1.48	1.8x10 ⁻¹²	1.38	1.26	1.51	4.2x10 ⁻¹³	0	N/A	N/A	N/A	N/A	N/A
SLC30A8	SLC30A8 p.Arg276Trp	rs13266634	8	118,184,783	C/T	0.691	1.09	1.08	1.11	1.9x10 ⁻⁴⁷	1.09	1.08	1.11	1.3x10 ⁻⁴⁷	0.683	1.12	1.1	1.14	8.2x10 ⁻³⁶	1
GPSM1	GPSM1 p.Ser391Leu	rs60980157	9	139,235,415	C/T	0.771	1.06	1.05	1.08	3.2x10 ⁻¹⁶	1.06	1.05	1.08	6.6x10 ⁻¹⁶	0.756	1.06	1.04	1.09	8.3x10 ⁻⁸	3
KCNJ11-ABCC8	KCNJ11 p.Lys29Glu	rs5219	11	17,409,572	T/C	0.364	1.06	1.05	1.07	5.7x10 ⁻²²	1.07	1.05	1.08	1.5x10 ⁻²²	0.381	1.07	1.05	1.09	8.1x10 ⁻¹⁶	1
CENTD2	ARAP1 p.Gln802Glu	rs56200889	11	72,408,055	G/C	0.733	1.04	1.02	1.05	4.8x10 ⁻⁸	1.05	1.03	1.06	5.2x10 ⁻¹⁰	0.727	1.05	1.03	1.07	2.3x10 ⁻⁸	2
KLHDC5	MRPS35 p.Gly43Arg	rs1127787	12	27,867,727	G/A	0.850	1.06	1.04	1.08	1.4x10 ⁻¹¹	1.05	1.03	1.07	1.5x10 ⁻⁸	0.842	1.06	1.04	1.09	2.2x10 ⁻⁷	2
HNF1A	HNF1A p.Ile75Leu	rs1169288	12	121,416,650	C/A	0.323	1.04	1.03	1.06	1.1x10 ⁻¹¹	1.04	1.02	1.06	1.9x10 ⁻¹⁰	0.33	1.05	1.04	1.07	4.6x10 ⁻⁹	1
	HNF1A p.Ala146Val	rs1800574	12	121,416,864	T/C	0.029	1.11	1.06	1.15	6.1x10 ⁻⁸	1.10	1.06	1.15	1.3x10 ⁻⁷	0.03	1.16	1.1	1.21	5.0x10 ⁻⁹	1
MPHOSPH9	SBNO1 p.Ser729Asn	rs1060105	12	123,806,219	C/T	0.815	1.04	1.02	1.06	5.7x10 ⁻⁷	1.04	1.02	1.06	1.1x10 ⁻⁷	0.787	1.04	1.02	1.06	3.6x10 ⁻⁵	2
CILP2	TM6SF2 p.Glu167Lys	rs58542926	19	19,379,549	T/C	0.076	1.07	1.05	1.10	4.8x10 ⁻¹²	1.09	1.06	1.11	3.4x10 ⁻¹⁵	0.076	1.09	1.05	1.12	2.0x10 ⁻⁷	1
GIPR	GIPR p.Glu318Gln	rs1800437	19	46,181,392	C/G	0.200	1.03	1.02	1.05	7.1x10 ⁻⁵	1.06	1.04	1.07	6.8x10 ⁻¹²	0.213	1.09	1.06	1.12	4.6x10 ⁻⁹	1
HNF4A	HNF4A p.Thr139Ile	rs1800961	20	43,042,364	T/C	0.032	1.09	1.05	1.13	2.6x10 ⁻⁸	1.10	1.06	1.14	5.0x10 ⁻⁸	0.037	1.17	1.12	1.22	1.4x10 ⁻¹²	1
MTMR3-ASCC2	ASCC2 p.Asp407His	rs28265	22	30,200,761	C/G	0.925	1.09	1.06	1.11	2.1x10 ⁻¹²	1.09	1.07	1.12	4.4x10 ⁻¹⁴	0.916	1.1	1.07	1.14	9.6x10 ⁻¹¹	3
Novel T2D associated loci																				
FAM63A	FAM63A p.Tyr95Asn	rs140386498	1	150,972,959	A/T	0.988	1.21	1.14	1.28	7.5x10 ⁻⁸	1.19	1.12	1.26	6.7x10 ⁻⁷	0.986	1.15	1.06	1.25	0.00047	3
CEP68	CEP68 p.Gly74Ser	rs7572857	2	65,296,798	G/A	0.846	1.05	1.04	1.07	8.3x10 ⁻⁹	1.05	1.03	1.07	6.6x10 ⁻⁷	0.830	1.06	1.03	1.08	6.6x10 ⁻⁷	2
KIF9	KIF9 p.Arg638Trp	rs2276853	3	47,282,303	A/G	0.588	1.02	1.01	1.04	8.0x10 ⁻⁵	1.03	1.02	1.05	5.3x10 ⁻⁸	0.602	1.04	1.02	1.05	2.6x10 ⁻⁵	3
ANKH	ANKH p.Arg187Gln	rs146886108	5	14,751,305	C/T	0.996	1.29	1.16	1.45	1.4x10 ⁻⁷	1.27	1.13	1.41	3.5x10 ⁻⁷	0.995	1.51	1.29	1.77	3.5x10 ⁻⁷	1
POC5	POC5 p.His36Arg	rs2307111	5	75,003,678	T/C	0.562	1.05	1.04	1.07	1.6x10 ⁻¹⁵	1.03	1.01	1.04	2.1x10 ⁻⁵	0.606	1.06	1.05	1.08	1.1x10 ⁻¹²	1
LPL	LPL p.Ser474*	rs328	8	19,819,724	C/G	0.903	1.05	1.03	1.08	6.8x10 ⁻⁹	1.05	1.03	1.07	2.3x10 ⁻⁷	0.901	1.08	1.05	1.11	7.1x10 ⁻⁸	1
PLCB3 [†]	PLCB3 p.Ser778Leu	rs35169799	11	64,031,241	T/C	0.071	1.05	1.02	1.08	1.3x10 ⁻⁵	1.06	1.03	1.09	1.8x10 ⁻⁷	0.065	1.07	1.04	1.11	3.8x10 ⁻⁵	1
TPCN2	TPCN2 p.Val219Ile	rs72928978	11	68,831,364	G/A	0.890	1.05	1.02	1.07	5.2x10 ⁻⁷	1.05	1.03	1.07	1.8x10 ⁻⁸	0.847	1.03	1.00	1.05	0.042	2
WSCD2	WSCD2 p.Thr113Ile	rs3764002	12	108,618,630	C/T	0.719	1.03	1.02	1.05	3.3x10 ⁻⁸	1.03	1.02	1.05	1.2x10 ⁻⁷	0.736	1.05	1.03	1.07	8.1x10 ⁻⁷	1
ZZEF1	ZZEF1 p.Ile402Val	rs781831	17	3,947,644	C/T	0.422	1.04	1.03	1.05	8.3x10 ⁻¹¹	1.03	1.02	1.05	1.8x10 ⁻⁷	0.407	1.04	1.02	1.05	2.1x10 ⁻⁵	2
MLX	MLX p.Gln139Arg	rs665268	17	40,722,029	G/A	0.294	1.04	1.02	1.05	2.0x10 ⁻⁸	1.03	1.02	1.04	1.1x10 ⁻⁵	0.280	1.04	1.02	1.06	5.2x10 ⁻⁶	2

<i>TTL6</i>	<i>TTL6</i> p.Glu712Asp	rs2032844	17	46,847,364	C/A	0.754	1.04	1.02	1.06	1.2x10 ⁻⁷	1.03	1.01	1.04	0.00098	0.750	1.04	1.02	1.06	9.5x10 ⁻⁵	3
<i>C17orf58</i> [†]	<i>C17orf58</i> p.Ile92Val	rs9891146	17	65,988,049	T/C	0.277	1.04	1.02	1.06	1.3x10 ⁻⁷	1.02	1.00	1.04	0.00058	0.269	1.05	1.03	1.07	1.7x10 ⁻⁷	2
<i>ZHX3</i> [†]	<i>ZHX3</i> p.Asn310Ser	rs17265513	20	39,832,628	C/T	0.211	1.05	1.03	1.07	9.2x10 ⁻⁸	1.04	1.02	1.05	2.9x10 ⁻⁶	0.208	1.02	1.00	1.04	0.068	N/A
<i>PNPLA3</i>	<i>PNPLA3</i> p.Ile148Met	rs738409	22	44,324,727	G/C	0.239	1.04	1.03	1.05	2.1x10 ⁻¹⁰	1.05	1.03	1.06	2.8x10 ⁻¹¹	0.230	1.05	1.03	1.07	5.8x10 ⁻⁶	1
<i>PIM3</i>	<i>PIM3</i> p.Val300Ala	rs4077129	22	50,356,693	T/C	0.276	1.04	1.02	1.05	1.9x10 ⁻⁷	1.04	1.02	1.06	3.5x10 ⁻⁸	0.280	1.04	1.02	1.06	8.7x10 ⁻⁵	3

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960 Chr: chromosome. Pos: Position build 37. RAF: risk allele frequency. R: risk allele. O: other allele. BMI: body mass index. OR: odds ratio. L95: lower 95% confidence interval.

961 U95: upper 95% confidence interval. GWAS: genome wide association studies.[†]Summary statistics from European ancestry specific meta-analyses of 48,286 cases and

962 250,671 controls. Fine-mapping group 1: signal is driven by coding variant, group 2: signal attributable to non-coding variants, and group 3: consistent with partial role for

963 coding variants. *p*-values are based on the meta-analyses of discovery stage and fine-mapping studies as appropriate.

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970 **Table 2 | Posterior probabilities for coding variants within 99% credible set across loci**
971 **with annotation-informed and functionally-unweighted prior based on fine-mapping**
972 **analysis performed using 50,160 T2D cases and 465,272 controls of European ancestry.**
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Locus	Variant	rs ID	Chr	Position	Posterior probability		Cumulative posterior probability attributed to coding variants	
					PPA	aiPPA	PPA	aiPPA
MACF1	MACF1 p.Ile39Val	rs16826069	1	39,797,055	0.012	0.240	0.032	0.628
	MACF1 p.Met1424Val	rs2296172	1	39,835,817	0.011	0.224		
	MACF1 p.Lys1625Asn	rs41270807	1	39,801,815	0.008	0.163		
FAM63A	FAM63A p.Tyr95Asn	rs140386498	1	150,972,959	0.005	0.129	0.012	0.303
GCKR	GCKR p. Pro 446Leu	rs1260326	2	27,730,940	0.773	0.995	0.773	0.995
THADA	THADA p.Cys845Tyr	rs35720761	2	43,519,977	<0.001	0.011	0.003	0.120
	THADA p.Thr897Ala	rs7578597	2	43,732,823	0.003	0.107		
CEP68	CEP68 p.Gly74Ser	rs7572857	2	65,296,798	<0.001	0.004	<0.001	0.004
GRB14	COBLL1 p.Asn901Asp	rs7607980	2	165,551,201	0.006	0.160	0.006	0.160
PPARG	PPARG p.Pro12Ala	rs1801282	3	12,393,125	0.023	0.410	0.024	0.410
KIF9	SETD2 p.Pro1962Lys	rs4082155	3	47,125,385	0.008	0.171	0.018	0.384
	NBEAL2 p.Arg511Gly	rs11720139	3	47,036,756	0.005	0.097		
	KIF9 p.Arg638Trp	rs2276853	3	47,282,303	0.003	0.059		
IGF2BP2	SEN2 p.Thr291Lys	rs6762208	3	185,331,165	<0.001	<0.001	<0.001	<0.001
WFS1	WFS1 p.Val333Ile	rs1801212	4	6,302,519	<0.001	0.001	<0.001	0.004
ANKH	ANKH p.Arg187Gln	rs146886108	5	14,751,305	0.459	0.972	0.447	0.972
POC5	POC5 p.His36Arg	rs2307111	5	75,003,678	0.697	0.954	0.702	0.986
PAM-PPIP5K2	PAM p.Asp336Gly	rs35658696	5	102,338,811	0.288	0.885	0.309	0.947
	PPIP5K2 p.Ser1207Gly	rs36046591	5	102,537,285	0.020	0.063		
RREB1 p.Asp1171Asn	RREB1 p.Asp1171Asn	rs9379084	6	7,231,843	0.920	0.997	0.920	0.997
RREB1 p.Ser1499Tyr	RREB1 p.Ser1499Tyr	rs35742417	6	7,247,344	<0.001	0.013	0.005	0.111
LPL	LPL p.Ser474*	rs328	8	19,819,724	0.023	0.832	0.023	0.832
SLC30A8	SLC30A8 p.Arg276Trp	rs13266634	8	118,184,783	0.295	0.823	0.295	0.823
GPSM1	GPSM1 p.Ser391Leu	rs60980157	9	139,235,415	0.031	0.557	0.031	0.557
KCNU11-ABCC8	KCNU11 p.Val250Ile	rs5215	11	17,408,630	0.208	0.412	0.481	0.951
	KCNU11 p.Lys29Glu	rs5219	11	17,409,572	0.190	0.376		
	ABCC8 p.Ala1369Ser	rs757110	11	17,418,477	0.083	0.163		
PLCB3	PLCB3 p.Ser778Leu	rs35169799	11	64,031,241	0.113	0.720	0.130	0.830
TPCN2	TPCN2 p.Val219Ile	rs72928978	11	68,831,364	<0.001	0.004	0.006	0.140
CENTD2	ARAP1 p.Gln802Glu	rs56200889	11	72,408,055	<0.001	<0.001	<0.001	<0.001
KLHDC5	MRPS35 p.Gly43Arg	rs1127787	12	27,867,727	<0.001	<0.001	<0.001	<0.001
WSCD2	WSCD2 p.Thr113Ile	rs3764002	12	108,618,630	0.281	0.955	0.282	0.958
HNF1A p.Ile75Leu	HNF1A Gly226Ala	rs56348580	12	121,432,117	0.358	0.894	0.358	0.894
	HNF1A p.Ile75Leu	rs1169288	12	121,416,650	<0.001	<0.001		
HNF1A p.Ala146Val	HNF1A p.Ala146Val	rs1800574	12	121,416,864	0.269	0.867	0.280	0.902
MPHOSPH9	SBN01 p.Ser729Asn	rs1060105	12	123,806,219	0.002	0.054	0.002	0.057
ZZEF1	ZZEF1 p.Ile402Val	rs781831	17	3,947,644	<0.001	0.001	<0.001	0.018
MLX	MLX p.Gln139Arg	rs665268	17	40,722,029	0.002	0.038	0.002	0.039
TTLL6	TTLL6 p.Glu712Asp	rs2032844	17	46,847,364	<0.001	<0.001	0.016	0.305
	CALCOCO2 p.Pro347Ala	rs10278	17	46,939,658	0.0100	0.187		
	SNF8 p.Arg155His	rs57901004	17	47,011,897	0.005	0.092		
C17orf58	C17orf58 p.Ile92Val	rs9891146	17	65,988,049	<0.001	0.009	<0.001	0.009
CILP2	TM6SF2 p.Glu167Lys	rs58542926	19	19,379,549	0.211	0.732	0.263	0.913
	TM6SF2 p.Leu156Pro	rs187429064	19	19,380,513	0.049	0.172		
GIPR	GIPR p.Glu318Gln	rs1800437	19	46,181,392	0.169	0.901	0.169	0.901
ZHX3	ZHX3 p.Asn310Ser	rs17265513	20	39,832,628	<0.001	0.003	0.003	0.110
HNF4A	HNF4A p.Thr139Ile	rs1800961	20	43,042,364	1.000	1.000	1.00	1.000
MTMR3-ASCC2	ASCC2 p.Asp407His	rs28265	22	30,200,761	0.011	0.192	0.028	0.481
	ASCC2 p.Pro423Ser	rs36571	22	30,200,713	0.007	0.116		
	ASCC2 p.Val123Ile	rs11549795	22	30,221,120	0.006	0.107		
	MTMR3 p.Asn960Ser	rs41278853	22	30,416,527	0.004	0.065		
PNPLA3	PNPLA3 p.Ile148Met	rs738409	22	44,324,727	0.112	0.691	0.130	0.806
	PARVB p.Trp37Arg	rs1007863	22	44,395,451	0.017	0.103		
PIM3	IL17REL p.Leu333Pro	rs5771069	22	50,435,480	0.041	0.419	0.047	0.475
	IL17REL p.Gly70Arg	rs9617090	22	50,439,194	0.005	0.054		
	PIM3 p.Val300Ala	rs4077129	22	50,356,693	<0.001	0.002		

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975 19th chromosome. Pos: Position build 37. PPA: functionally-unweighted prior; aiPPA: annotation informed prior. Index
976 coding variants are highlighted in bold.

ONLINE METHODS

Ethics statement. All human research was approved by the relevant institutional review boards, and conducted according to the Declaration of Helsinki. All participants provided written informed consent.

Derivation of significance thresholds. We considered five categories of annotation¹⁶ of variants on the exome array in order of decreasing effect on biological function: (1) PTVs (stop-gain and stop-loss, frameshift indel, donor and acceptor splice-site, and initiator codon variants, $n_1=8,388$); (2) moderate-impact variants (missense, in-frame indel, and splice region variants, $n_2=216,114$); (3) low-impact variants (synonymous, 3' and 5' UTR, and upstream and downstream variants, $n_3=8,829$); (4) other variants mapping to DNase I hypersensitive sites (DHS) in any of 217 cell types⁸ (DHS, $n_4=3,561$); and (5) other variants not mapping to DHS ($n_5=10,578$). To account for the greater prior probability of causality for variants with greater effect on biological function, we determined a weighted Bonferroni-corrected significance threshold on the basis of reported enrichment¹⁶, denoted w_i , in each annotation category, i : $w_1=165$; $w_2=33$; $w_3=3$; $w_4=1.5$; $w_5=0.5$. For coding variants (annotation categories 1 and 2):

$$\alpha = \frac{0.05 \sum_{i=1}^2 n_i w_i}{(\sum_{i=1}^2 n_i)(\sum_{i=1}^5 n_i w_i)} = 2.21 \times 10^{-7}.$$

We note that this threshold is similar to a simple Bonferroni correction for the total number of coding variants on the array, which would yield:

$$\alpha = \frac{0.05}{224502} = 2.23 \times 10^{-7}.$$

For non-coding variants (annotation categories 3, 4 and 5) the weighted Bonferroni-corrected significance threshold is:

$$\alpha = \frac{0.05 \sum_{i=3}^5 n_i w_i}{(\sum_{i=3}^5 n_i)(\sum_{i=1}^5 n_i w_i)} = 9.45 \times 10^{-9}.$$

DISCOVERY: Exome-array study-level analyses. Within each study, genotype calling and quality control were undertaken according to protocols developed by the UK Exome Chip Consortium or the CHARGE central calling effort³⁸ (**Supplementary Table 1**). Within each study, variants were then excluded for the following reasons: (i) not mapping to autosomes or X chromosome; (ii) multi-allelic and/or insertion-deletion; (iii) monomorphic; (iv) call rate <99%; or (v) exact $p < 10^{-4}$ for deviation from Hardy-Weinberg equilibrium (autosomes only).

We tested association of T2D with each variant in a linear mixed model, implemented in RareMetalWorker¹⁷, using a genetic relationship matrix (GRM) to account for population structure and relatedness. For participants from family-based studies, known relationships were incorporated directly in the GRM. For founders and participants from population-based studies, the GRM was constructed from pair-wise identity by descent (IBD) estimates based on LD pruned ($r^2 < 0.05$) autosomal variants with MAF $\geq 1\%$ (across cases and controls combined), after exclusion of those in high LD and complex regions^{39,40}, and those mapping to established T2D loci. We considered additive, dominant, and recessive models for the effect of the minor allele, adjusted for age and sex (where appropriate) and additional study-specific covariates (**Supplementary Table 2**). Analyses were also performed with and without adjustment for BMI (where available Supplementary Table 2).

For single-variant association analyses, variants with minor allele count ≤ 10 in cases and controls combined were excluded. Association summary statistics for each analysis were corrected for residual inflation by means of genomic control⁴¹, calculated after excluding variants mapping to established T2D susceptibility loci. For gene-based analyses, we made no variant exclusions on the basis of minor allele count.

DISCOVERY: Exome-sequence analyses. We used summary statistics of T2D association from analyses conducted on 8,321 T2D cases and 8,421 controls across different ancestries, all genotyped using exome sequencing. Details of samples included, sequencing, and quality control are described elsewhere^{12,15} (<http://www.type2diabetesgenetics.org/>). Samples were subdivided into 15 sub-groups according to ancestry and study of origin. Each sub-group was analysed independently, with sub-group specific principal components and genetic relatedness matrices. Association tests were performed with both a linear mixed model, as implemented in EMMAX⁴², using covariates for sequencing batch, and the Firth

test, using covariates for principal components and sequencing batch. Related samples were excluded from the Firth analysis but maintained in the linear mixed model analysis. Variants were then filtered from each sub-group analysis, according to call rate, differential case-control missing-ness, or deviation from Hardy-Weinberg equilibrium (as computed separately for each sub-group). Association statistics were then combined via a fixed-effects inverse-variance weighted meta-analysis, at both the level of ancestry as well as across all samples. P-values were taken from the linear mixed model analysis, while effect sizes estimates were taken from the Firth analysis. Analyses were performed with and without adjustment for BMI. From exome sequence summary statistics, we extracted variants passing quality control and present on the exome array.

DISCOVERY: GWAS analyses. The UK Biobank is a large detailed prospective study of more than 500,000 participants aged 40-69 years when recruited in 2006-2010¹³. Prevalent T2D status was defined using self-reported medical history and medication in UK Biobank participants⁴³. Participants were genotyped with the UK Biobank Axiom Array or UK BiLEVE Axiom Array, and quality control and population structure analyses were performed centrally at UK Biobank. We defined a subset of “white European” ancestry samples (n=120,286) as those who both self-identified as white British and were confirmed as ancestrally “Caucasian” from the first two axes of genetic variation from principal components analysis. Imputation was also performed centrally at UK Biobank for the autosomes only, up to a merged reference panel from the 1000 Genomes Project (multi-ethnic, phase 3, October 2014 release)⁴⁴ and the UK10K Project⁹. We used SNPTESTv2.5⁴⁵ to test for association of T2D with each SNP in a logistic regression framework under an additive model, and after adjustment for age, sex, six axes of genetic variation, and genotyping array as covariates. Analyses were performed with and without adjustment for BMI, after removing related individuals.

GERA is a large multi-ethnic population-based cohort, created for investigating the genetic and environmental basis of age-related diseases [dbGaP phs000674.p1]. T2D status is based on ICD-9 codes in linked electronic medical health records, with all other participants defined as controls. Participants have previously been genotyped using one of four custom arrays, which have been designed to maximise coverage of common and low-frequency variants in non-Hispanic white, East Asian, African American, and Latino

ethnicities^{46,47}. Methods for quality control have been described previously¹⁴. Each of the four genotyping arrays were imputed separately, up to the 1000 Genomes Project reference panel (autosomes, phase 3, October 2014 release; X chromosome, phase 1, March 2012 release) using IMPUTEv2.3^{48,49}. We used SNPTESTv2.5⁴⁵ to test for association of T2D with each SNP in a logistic regression framework under an additive model, and after adjustment for sex and nine axes of genetic variation from principal components analysis as covariates. BMI was not available for adjustment in GERA.

For UK Biobank and GERA, we extracted variants passing standard imputation quality control thresholds (IMPUTE info \geq 0.4)⁵⁰ and present on the exome array. Association summary statistics under an additive model were corrected for residual inflation by means of genomic control⁴¹, calculated after excluding variants mapping to established T2D susceptibility loci: GERA (λ =1.097 for BMI unadjusted analysis) and UK Biobank (λ =1.043 for BMI unadjusted analysis, λ =1.056 for BMI adjusted analysis).

DISCOVERY: Single-variant meta-analysis. We aggregated association summary statistics under an additive model across studies, with and without adjustment for BMI, using METAL⁵¹: (i) effective sample size weighting of Z-scores to obtain *p*-values; and (ii) inverse variance weighting of log-odds ratios. For exome-array studies, allelic effect sizes and standard errors obtained from the RareMetalWorker linear mixed model were converted to the log-odds scale prior to meta-analysis to correct for case-control imbalance⁵².

The European-specific meta-analyses aggregated association summary statistics from a total of 48,286 cases and 250,671 controls from: (i) 33 exome-array studies of European ancestry; (ii) exome-array sequence from individuals of European ancestry; and (iii) GWAS from UK Biobank. Note that non-coding variants represented on the exome array were not available in exome sequence. The European-specific meta-analyses were corrected for residual inflation by means of genomic control⁴¹, calculated after excluding variants mapping to established T2D susceptibility loci: λ =1.091 for BMI unadjusted analysis and λ =1.080 for BMI adjusted analysis.

The trans-ethnic meta-analyses aggregated association summary statistics from a total of 81,412 cases and 370,832 controls across all studies (51 exome array studies, exome sequence, and GWAS from UK Biobank and GERA), irrespective of ancestry. Note that non-coding variants represented on the exome array were not available in exome sequence. The

trans-ethnic meta-analyses were corrected for residual inflation by means of genomic control⁴¹, calculated after excluding variants mapping to established T2D susceptibility loci: $\lambda=1.073$ for BMI unadjusted analysis and $\lambda=1.068$ for BMI adjusted analysis. Heterogeneity in allelic effect sizes between exome-array studies contributing to the trans-ethnic meta-analysis was assessed by Cochran's Q statistic⁵³.

DISCOVERY: Detection of distinct association signals. Conditional analyses were undertaken to detect association signals by inclusion of index variants and/or tags for previously reported non-coding GWAS lead SNPs as covariates in the regression model at the study level. Within each exome-array study, approximate conditional analyses were undertaken under a linear mixed model using RareMetal¹⁷, which uses score statistics and the variance-covariance matrix from the RareMetalWorker single-variant analysis to estimate the correlation in effect size estimates between variants due to LD. Study-level allelic effect sizes and standard errors obtained from the approximate conditional analyses were converted to the log-odds scale to correct for case-control imbalance⁵². Within each GWAS, exact conditional analyses were performed under a logistic regression model using SNPTTESTv2.5⁴⁵. GWAS variants passing standard imputation quality control thresholds (IMPUTE info ≥ 0.4)⁵⁰ and present on the exome array were extracted for meta-analysis.

Association summary statistics were aggregated across studies, with and without adjustment for BMI, using METAL⁵¹: (i) effective sample size weighting of Z-scores to obtain p -values; and (ii) inverse variance weighting of log-odds ratios.

We defined novel loci as mapping >500kb from a previously reported lead GWAS SNP. We performed conditional analyses where a novel signal mapped close to a known GWAS locus, and the lead GWAS SNP at that locus is present (or tagged) on the exome array (**Supplementary Table 5**).

DISCOVERY: Non-additive association models. For exome-array studies only, we aggregated association summary statistics under recessive and dominant models across studies, with and without adjustment for BMI, using METAL⁵¹: (i) effective sample size weighting of Z-scores to obtain p -values; and (ii) inverse variance weighting of log-odds ratios. Allelic effect sizes and standard errors obtained from the RareMetalWorker linear mixed model were converted to the log-odds scale prior to meta-analysis to correct for case-control

imbalance⁵². The European-specific meta-analyses aggregated association summary statistics from a total of 41,066 cases and 136,024 controls from 33 exome-array studies of European ancestry. The European-specific meta-analyses were corrected for residual inflation by means of genomic control⁴¹, calculated after excluding variants mapping to established T2D susceptibility loci: $\lambda=1.076$ and $\lambda=1.083$ for BMI unadjusted analysis, under recessive and dominant models respectively, and $\lambda=1.081$ and $\lambda=1.062$ for BMI adjusted analysis, under recessive and dominant models respectively. The trans-ethnic meta-analyses aggregated association summary statistics from a total of 58,425 cases and 188,032 controls across all exome-array studies, irrespective of ancestry. The trans-ethnic meta-analyses were corrected for residual inflation by means of genomic control⁴¹, calculated after excluding variants mapping to established T2D susceptibility loci: $\lambda=1.041$ and $\lambda=1.071$ for BMI unadjusted analysis, under recessive and dominant models respectively, and $\lambda=1.031$ and $\lambda=1.063$ for BMI adjusted analysis, under recessive and dominant models respectively.

DISCOVERY: Gene-based meta-analyses. For exome-array studies only, we aggregated association summary statistics under an additive model across studies, with and without adjustment for BMI, using RareMetal¹⁷. This approach uses score statistics and the variance-covariance matrix from the RareMetalWorker single-variant analysis to estimate the correlation in effect size estimates between variants due to LD. We performed gene-based analyses using a burden test (assuming all variants have same direction of effect on T2D susceptibility) and SKAT (allowing variants to have different directions of effect on T2D susceptibility). We used two previously defined filters for annotation and MAF¹⁸ to define group files: (i) strict filter, including 44,666 variants; and (ii) broad filter, including all variants from the strict filter, and 97,187 additional variants.

We assessed the contribution of each variant to gene-based signals by performing approximate conditional analyses. We repeated RareMetal analyses for the gene, excluding each variant in turn from the group file, and compared the strength of the association signal.

Fine-mapping of coding variant association signals with T2D susceptibility. We defined a locus as mapping 500kb up- and down-stream of each index coding variant (**Supplementary Table 5**), excluding the MHC. Our fine-mapping analyses aggregated association summary

statistics from 24 GWAS incorporating 50,160 T2D cases and 465,272 controls of European ancestry from the DIAGRAM Consortium (**Supplementary Table 9**). Each GWAS was imputed using miniMAC¹² or IMPUTEv2^{48,49} up to high-density reference panels: (i) 22 GWAS were imputed up to the Haplotype Reference Consortium²⁰; (ii) the UK Biobank GWAS was imputed to a merged reference panel from the 1000 Genomes Project (multi-ethnic, phase 3, October 2014 release)⁴⁴ and the UK10K Project⁹; and (iii) the deCODE GWAS was imputed up to the deCODE Icelandic population-specific reference panel based on whole-genome sequence data¹⁹. Association with T2D susceptibility was tested for each remaining variant using logistic regression, adjusting for age, sex, and study-specific covariates, under an additive genetic model. Analyses were performed with and without adjustment for BMI. For each study, variants with minor allele count<5 (in cases and controls combined) or those with imputation quality $r^2\text{-hat}<0.3$ (miniMAC) or proper-info<0.4 (IMPUTE2) were removed. Association summary statistics for each analysis were corrected for residual inflation by means of genomic control⁴¹, calculated after excluding variants mapping to established T2D susceptibility loci.

We aggregated association summary statistics across studies, with and without adjustment for BMI, in a fixed-effects inverse variance weighted meta-analysis, using METAL⁵¹. The BMI unadjusted meta-analysis was corrected for residual inflation by means of genomic control ($\lambda=1.012$)⁴¹, calculated after excluding variants mapping to established T2D susceptibility loci. No adjustment was required for BMI adjusted meta-analysis ($\lambda=0.994$). From the meta-analysis, variants were extracted that were present on the HRC panel and reported in at least 50% of total effective sample size.

We included 37 of the 40 identified coding variants in fine-mapping analyses, excluding three that were not amenable to fine-mapping in the GWAS data sets: (i) the locus in the major histocompatibility complex because of the extended and complex structure of LD across the region, which complicates fine-mapping efforts; (ii) the East Asian specific *PAX4* p.Arg190His (rs2233580) signal, since the variant was not present in European ancestry GWAS; and (iii) *ZHX3* p.Asn310Ser (rs4077129) because the variant was only weakly associated with T2D in the GWAS data sets used for fine-mapping.

To delineate distinct association signals in four regions, we undertook approximate conditional analyses, implemented in GCTA⁵⁴, to adjust for the index coding variants and non-coding lead GWAS SNPs: (i) *RREB1* p. Asp1171Asn (rs9379084), p.Ser1499Tyr

(rs35742417), and rs9505118; (ii) *HNF1A* p.Ile75Leu (rs1169288) and p.Ala146Val (rs1800574); (iii) *GIPR* p.Glu318Gln (rs1800437) and rs8108269; and (iv) *HNF4A* p.Thr139Ile (rs1800961) and rs4812831. We made use of summary statistics from the fixed-effects meta-analyses (BMI unadjusted for *RREB1*, *HNF1A*, and *HNF4A*, and BMI adjusted for *GIPR* as this signal was only seen in BMI adjusted analysis) and genotype data from 5,000 random individuals of European ancestry from the UK Biobank, as reference for LD between genetic variants across the region.

For each association signal, we first calculated an approximate Bayes' factor⁵⁵ in favour of association on the basis of allelic effect sizes and standard errors from the meta-analysis. Specifically, for the j th variant,

$$\Lambda_j = \sqrt{\frac{V_j}{V_j + \omega}} \exp \left[\frac{\omega \beta_j^2}{2V_j(V_j + \omega)} \right],$$

where β_j and V_j denote the estimated allelic effect (log-OR) and corresponding variance from the meta-analysis. The parameter ω denotes the prior variance in allelic effects, taken here to be 0.04⁵⁵.

We then calculated the posterior probability that the j th variant drives the association signal, given by

$$\pi_j = \frac{\rho_j \Lambda_j}{\sum_k \rho_k \Lambda_k}.$$

In this expression, ρ_j denotes the prior probability that the j th variant drives the association signal, and the summation in the denominator is over all variants across the locus. We considered two prior models: (i) functionally unweighted, for which $\rho_j = 1$ for all variants; and (ii) annotation informed, for which ρ_j is determined by the functional severity of the variant. For the annotation informed prior, we considered five categories of variation¹⁶, such that: (i) $\rho_j = 165$ for PTVs; (ii) $\rho_j = 33$ for moderate-impact variants; (iii) $\rho_j = 3$ for low-impact variants; (iv) $\rho_j = 1.5$ for other variants mapping to DHS; and (v) $\rho_j = 0.5$ for all other variants.

For each locus, the 99% credible set²¹ under each prior was then constructed by: (i) ranking all variants according to their posterior probability of driving the association signal;

and (ii) including ranked variants until their cumulative posterior probability of driving the association attained or exceeded 0.99.

Functional impact of coding alleles. We used CADD³⁴ to obtain scaled Combined Annotation Dependent Depletion score (CADD-score) for each of the 40 significantly associated coding variants. The CADD method objectively integrates a range of different annotation metrics into a single measure (CADD-score), providing an estimate of deleteriousness for all known variants and an overall rank for this metric across the genome. We obtained the estimates of the intolerance of a gene to harbouring loss-of-function variants (pLI) from the ExAC data set³³. We used the Kolmogorov-Smirnov test to determine whether fine-mapping groups 1 and 2 have the same statistical distribution for each of these parameters.

T2D loci and physiological classification. To explore the different patterns of association between T2D and other anthropometric/metabolic/endocrine traits and diseases, we performed hierarchical clustering analysis. We obtained association summary statistics for a range of metabolic traits and other outcomes for 94 coding and non-coding variants that were significantly associated with T2D through collaboration or by querying publically available GWAS meta-analysis datasets. The z-score (allelic effect/SE) was aligned to the T2D-risk allele. We obtained the distance matrix amongst z-score of the loci/traits using the Euclidean measure and performed clustering using the complete agglomeration method. Clustering was visualised by constructing a dendrogram and heatmap.

DATA AVAILABILITY STATEMENT

Summary level data of the exome-array component of this project can be downloaded from the DIAGRAM consortium website <http://diagram-consortium.org/> and Accelerating Medicines Partnership T2D portal <http://www.type2diabetesgenetics.org/>.

MATERIALS & CORRESPONDENCE

Correspondence and requests for materials should be addressed to mark.mccarthy@drl.ox.ac.uk and anubha@well.ox.ac.uk. Reprints and permissions information is available at www.nature.com/reprints.

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1304 **URLs**

1305 Type 2 Diabetes Knowledge Portal: <http://www.type2diabetesgenetics.org/>

Refining the accuracy of validated target identification through coding variant fine-mapping in type 2 diabetes

Mahajan *et al.* *

*A full list of co-authors names appears in the main paper

SUPPLEMENTARY NOTES

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ii. Supplementary Tables

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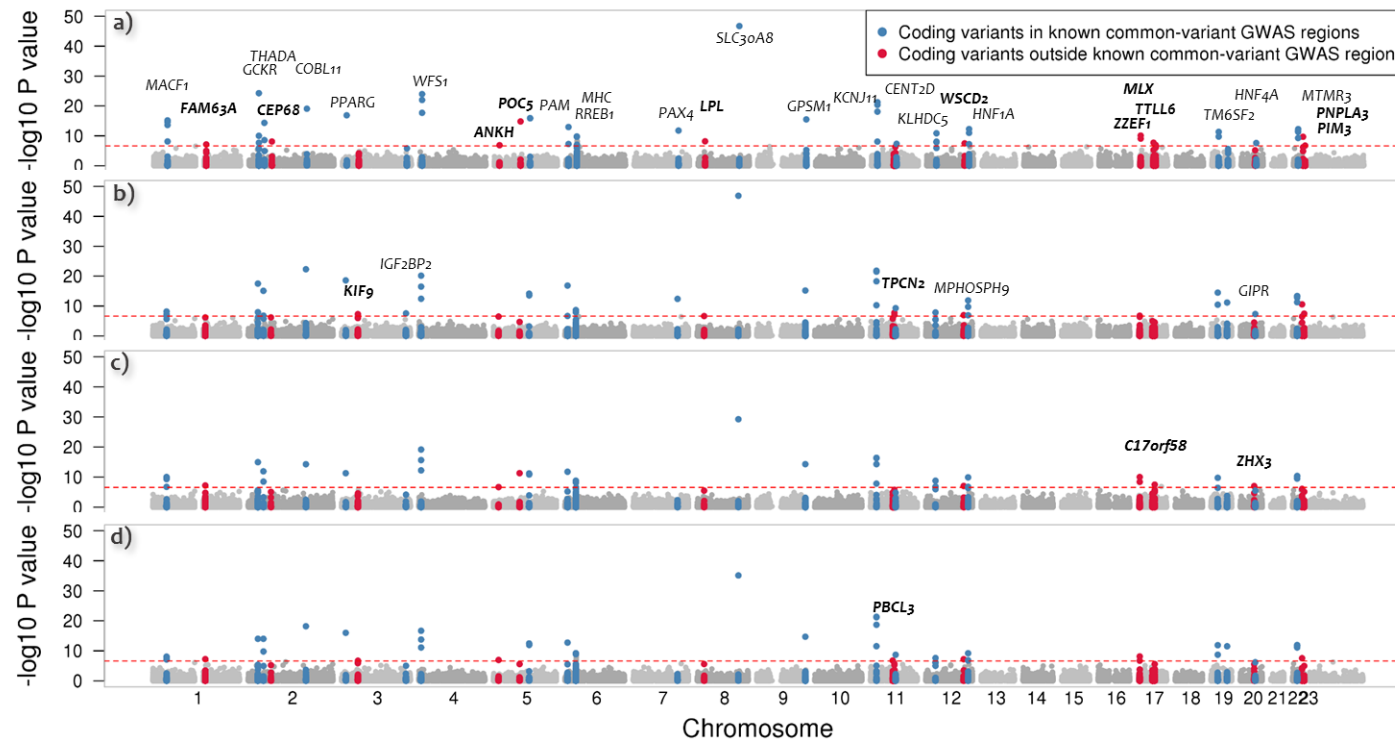
- **Supplementary Table 4** | Summary statistics for additive, recessive and dominant models for coding variants attaining exome-wide significant evidence ($p < 2.2 \times 10^{-7}$) of association with T2D susceptibility in the discovery analysis.
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- **Supplementary Table 7** | Lead SNPs for non-coding T2D association signals attaining genome-wide significance ($p < 5 \times 10^{-8}$) that map outside previously established susceptibility loci.
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iii. Grants, funding support and acknowledgements for individuals and studies

iv. Consortium membership

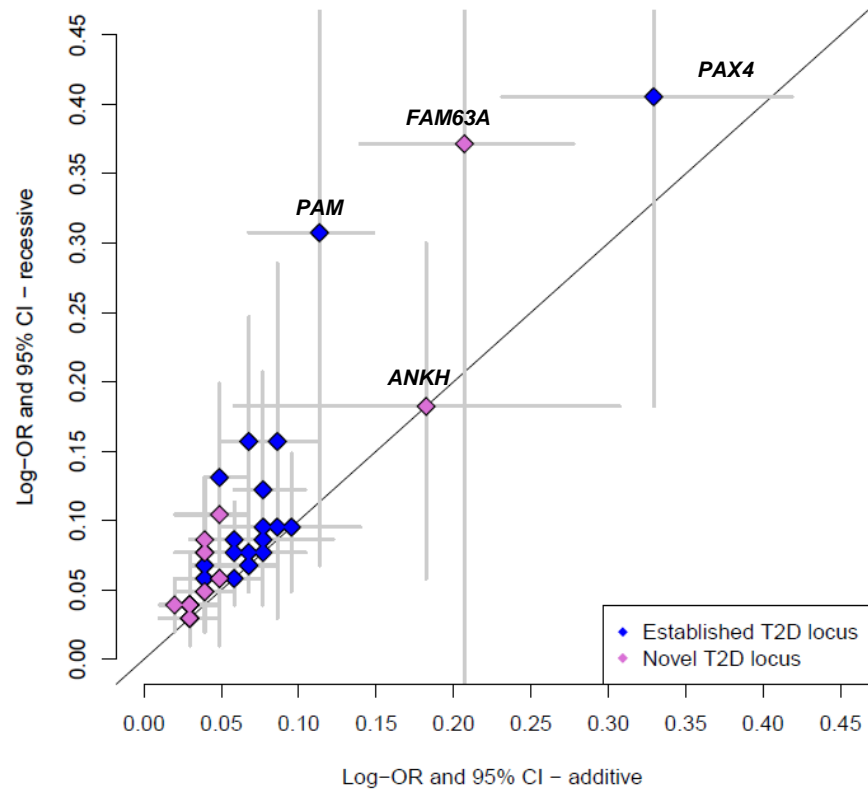
i. Supplementary Figures

Supplementary Figure 1 | Manhattan plots of coding variants associated with type 2 diabetes in discovery analysis. The x-axis represents chromosomal location, and the y-axis represents the $-\log_{10} p$ -value for tests of association between SNPs and T2D. The dashed line represents exome-wide significance at $p=2.2 \times 10^{-7}$. Coding variants in known, common-variant GWAS regions are shown in blue; and variants outside common-variant GWAS regions are shown in red. Coding association signals mapping outside regions previously implicated in T2D susceptibility, defined as >500kb from the reported lead GWAS SNPs are highlighted in bold. Plots are shown by ancestry and with and without BMI adjustment: **a)** trans-ethnic meta-analyses of 81,412 cases and 370,832 controls, **b)** trans-ethnic meta-analyses adjusted for BMI of 68,048 cases and 304,612 controls, **c)** European-specific of 48,286 cases and 250,671 controls, **d)** European-specific adjusted for BMI of 47,181 cases and 249,280 controls.

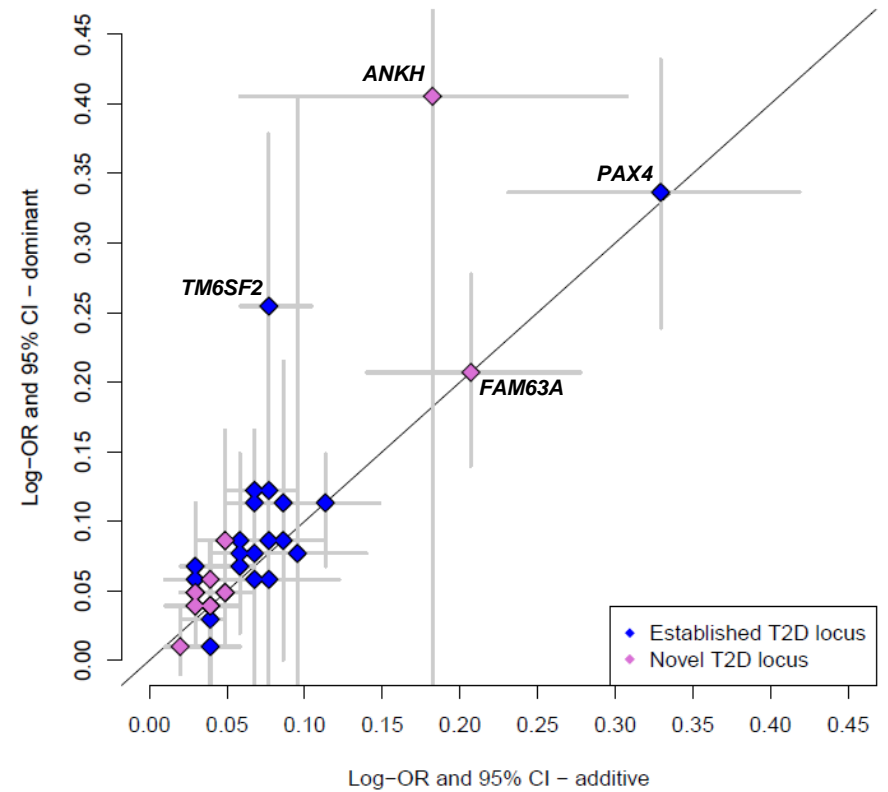


Supplementary Figure 2 | Plots of allelic effect sizes by mode of inheritance. Allelic effects sizes from additive model against: **a)** recessive and **b)** dominant models estimated in trans-ethnic meta-analyses of 58,425 cases and 188,032. Each point represents a coding variant with the log-OR and 95% CI from the additive model plotted on the x-axis and the log-OR and 95% CI from recessive or dominant model plotted on the y-axis. Novel coding association signals are coloured pink and coding variant signals within established T2D risk loci are coloured blue.

a)

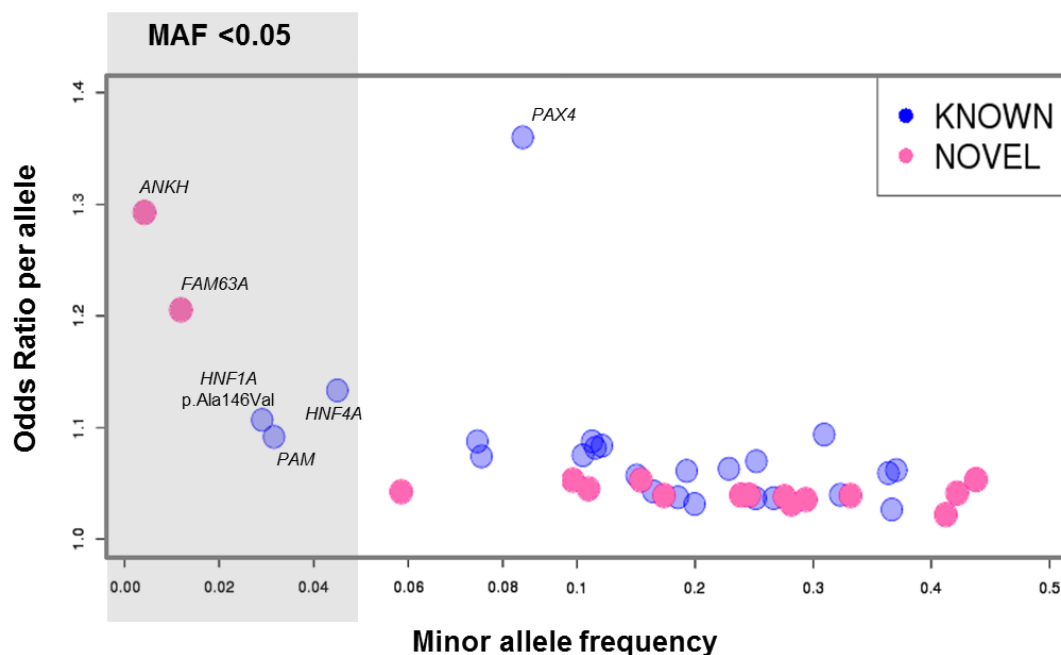


b)

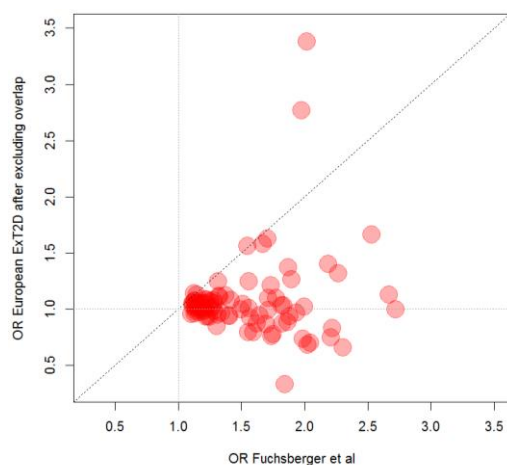


Supplementary Figure 3 | Contribution of low-frequency and rare coding variation to T2D susceptibility. a) Allelic effects sizes of the 40 coding association signals from additive models are plotted against minor allele frequency. Known variants are shown in blue; and novel variants are shown in pink. Variants with a minor allele frequency <0.05 are highlighted in grey. (b-c) Fuchsberger *et al.*¹ observed 100 low-frequency coding variants with modest effects (allelic OR 1.10-2.66) for which the association evidence was strong but not genome-wide significant. The European-specific OR of these 100 low-frequency coding variants from Fuchsberger *et al.* was compared to the European-specific ORs from this study (ExtT2D): **b)** ORs from Fuchsberger *et al.* plotted on the x-axis and OR from European ExtT2D samples after removing overlapping samples. **c)** ORs from Fuchsberger *et al.* plotted on the x-axis and OR from all European ExtT2D samples. ¹ Fuchsberger, C. *et al.* The genetic architecture of type 2 diabetes. *Nature* **536**, 41-7 (2016).

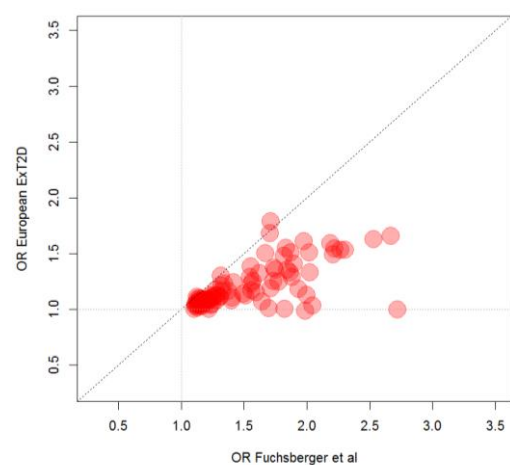
a)



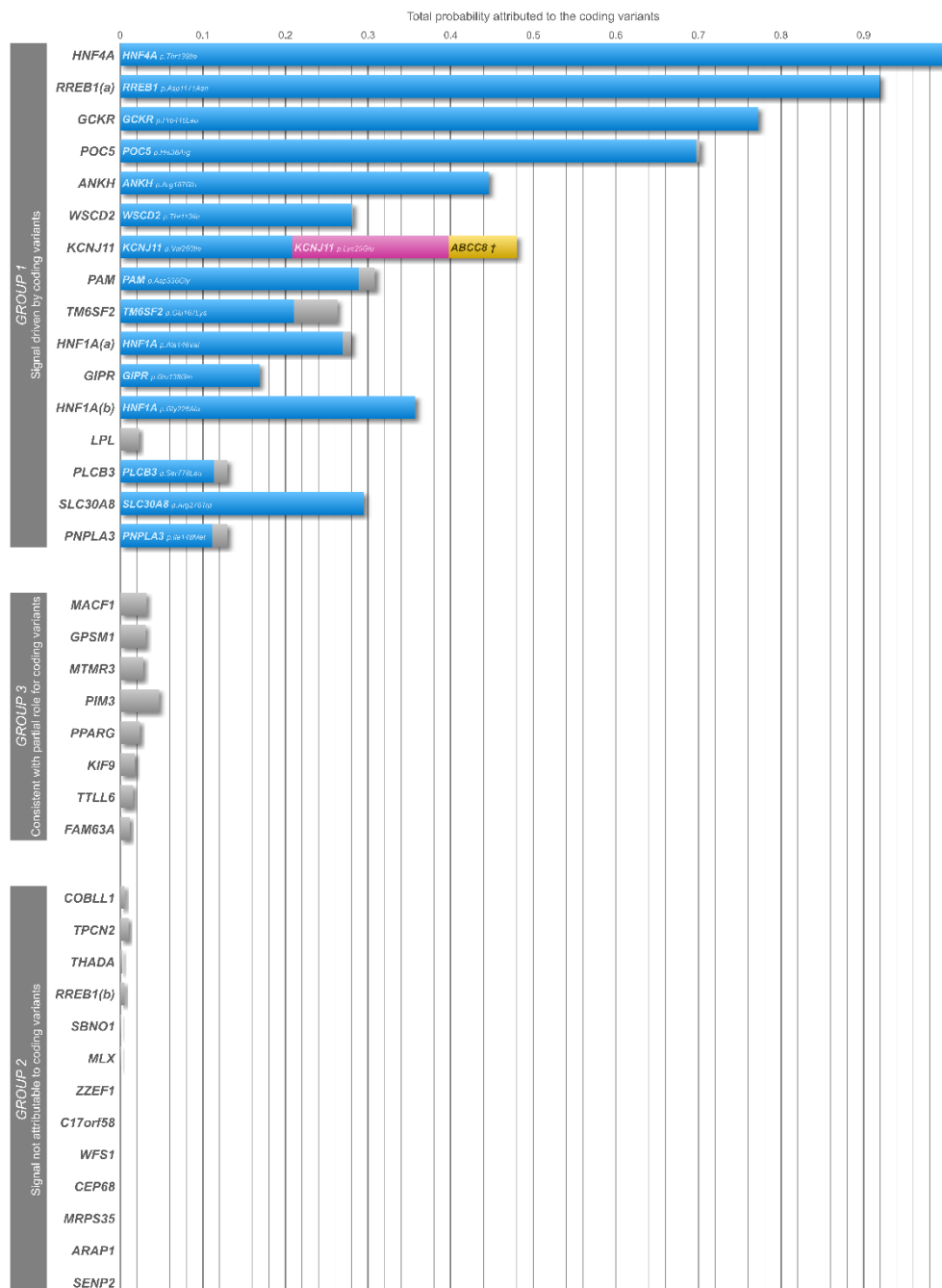
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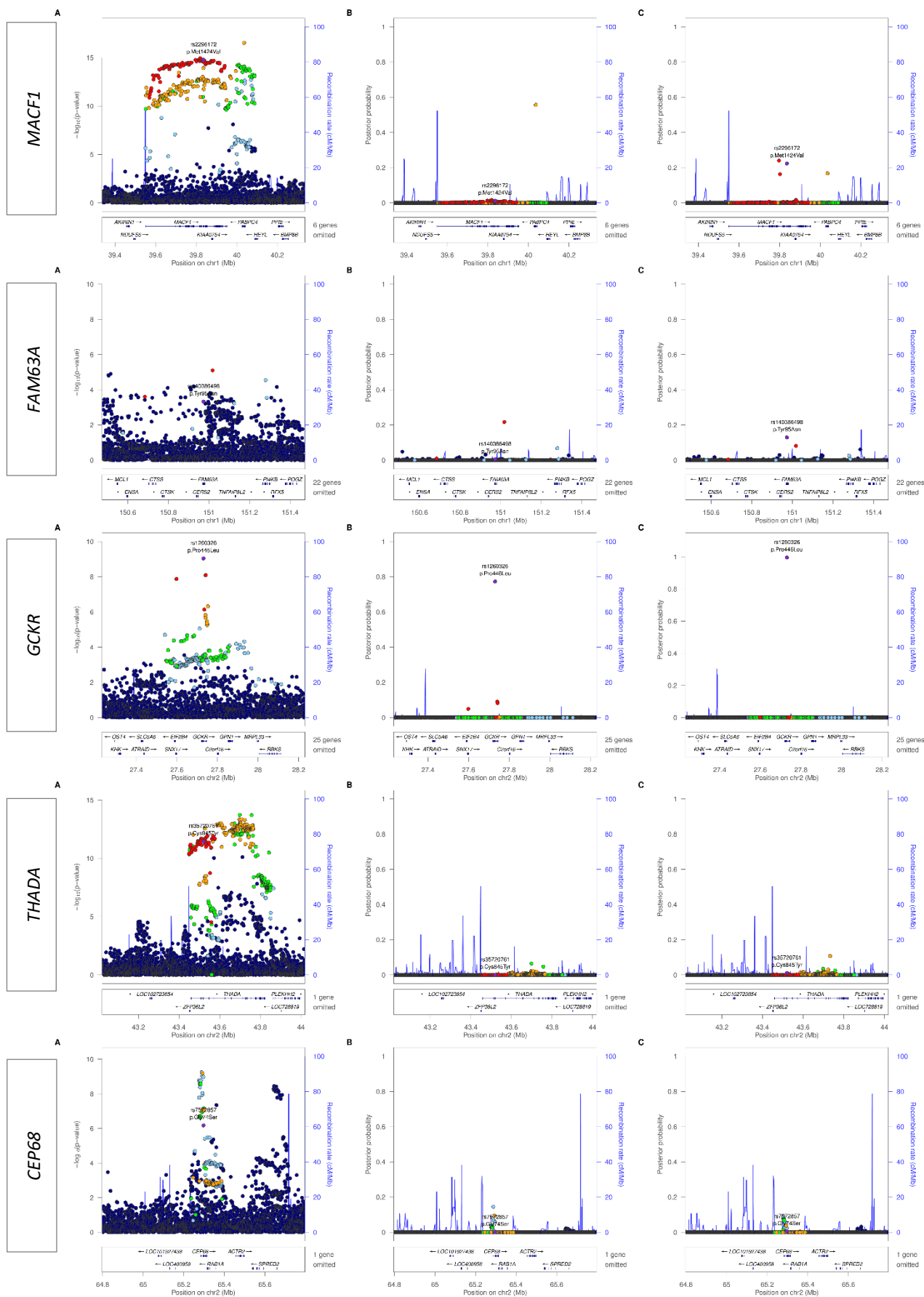
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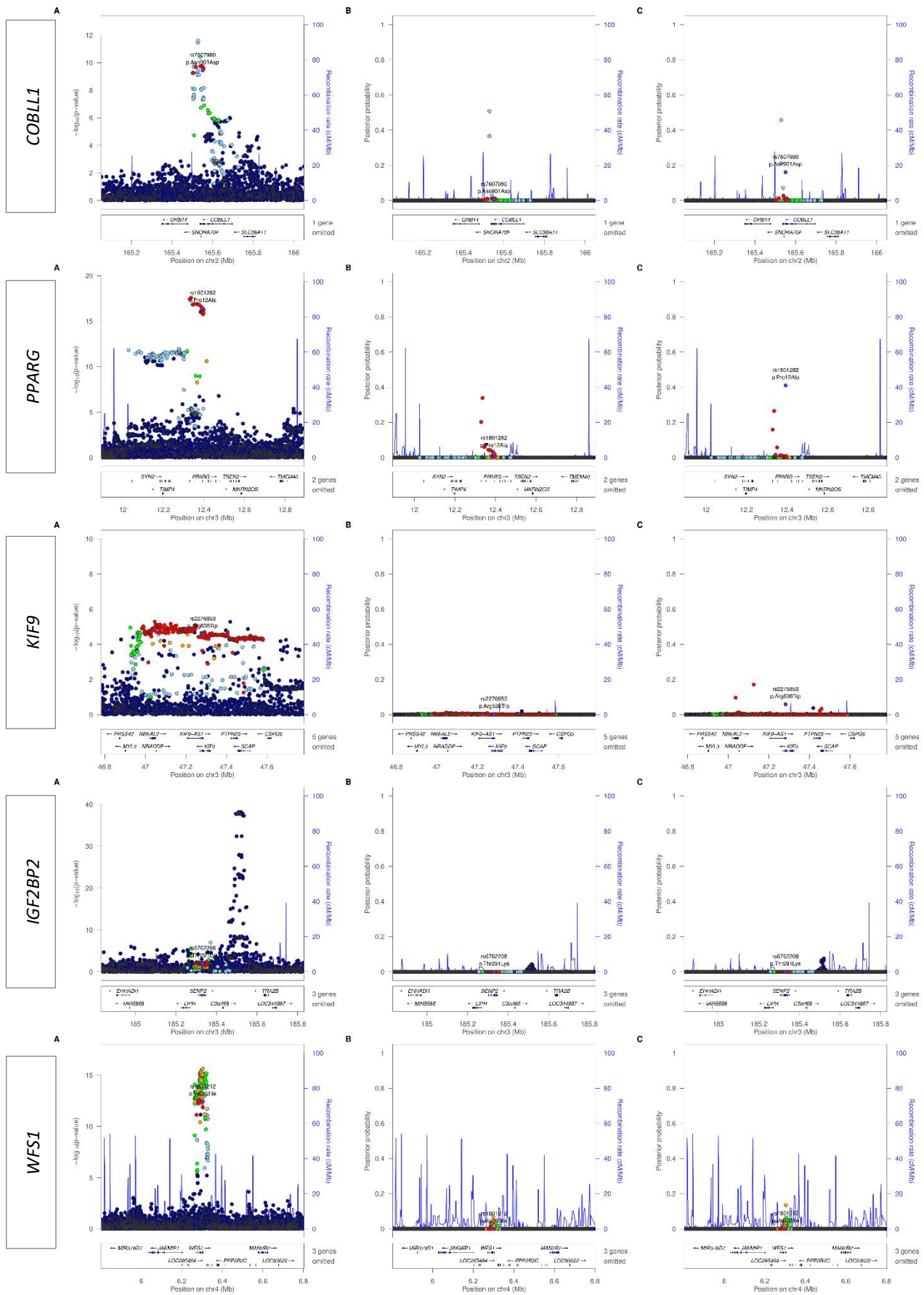


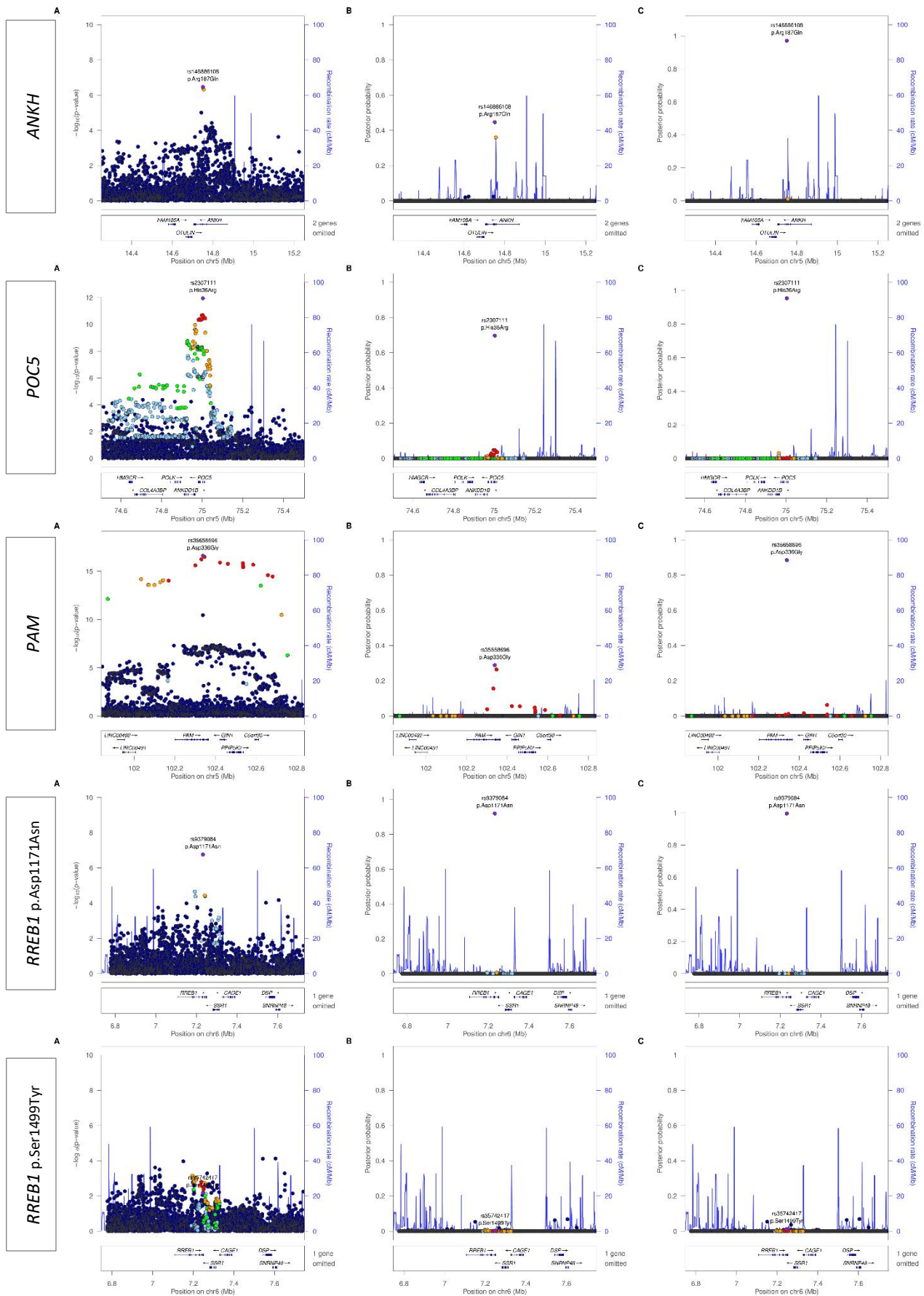
Supplementary Figure 4 | Posterior probabilities for coding variants across loci with functionally unweighted priors. Fine-mapping of 37 distinct association signals was performed using European ancestry GWAS meta-analysis including 50,160 T2D cases and 465,272 controls. For each signal, we constructed a credible set of variants accounting for 99% of the posterior probability of driving the association. Each bar here represents a signal with the total probability attributed to the coding variants within the 99% credible set plotted on the y-axis. When the probability (bar) is split across multiple coding variants (at least 0.05 probability attributed to a variant) at a particular locus, these are indicated by blue, pink, and yellow. The combined probability of the remaining coding variants is highlighted in grey. *RREB1(a)*: *RREB1* p.Asp1171Asn; *RREB1(b)*: *RREB1* p.Ser1499Tyr; *HNF1A(a)*: *HNF1A* p.Ala146Val; *HNF1A(b)*: *HNF1A* p.Ile75Leu; *ABCC8†*: *ABCC8* p.Ala1369Ser. Note that the groups are defined based on the annotation-informed priors.

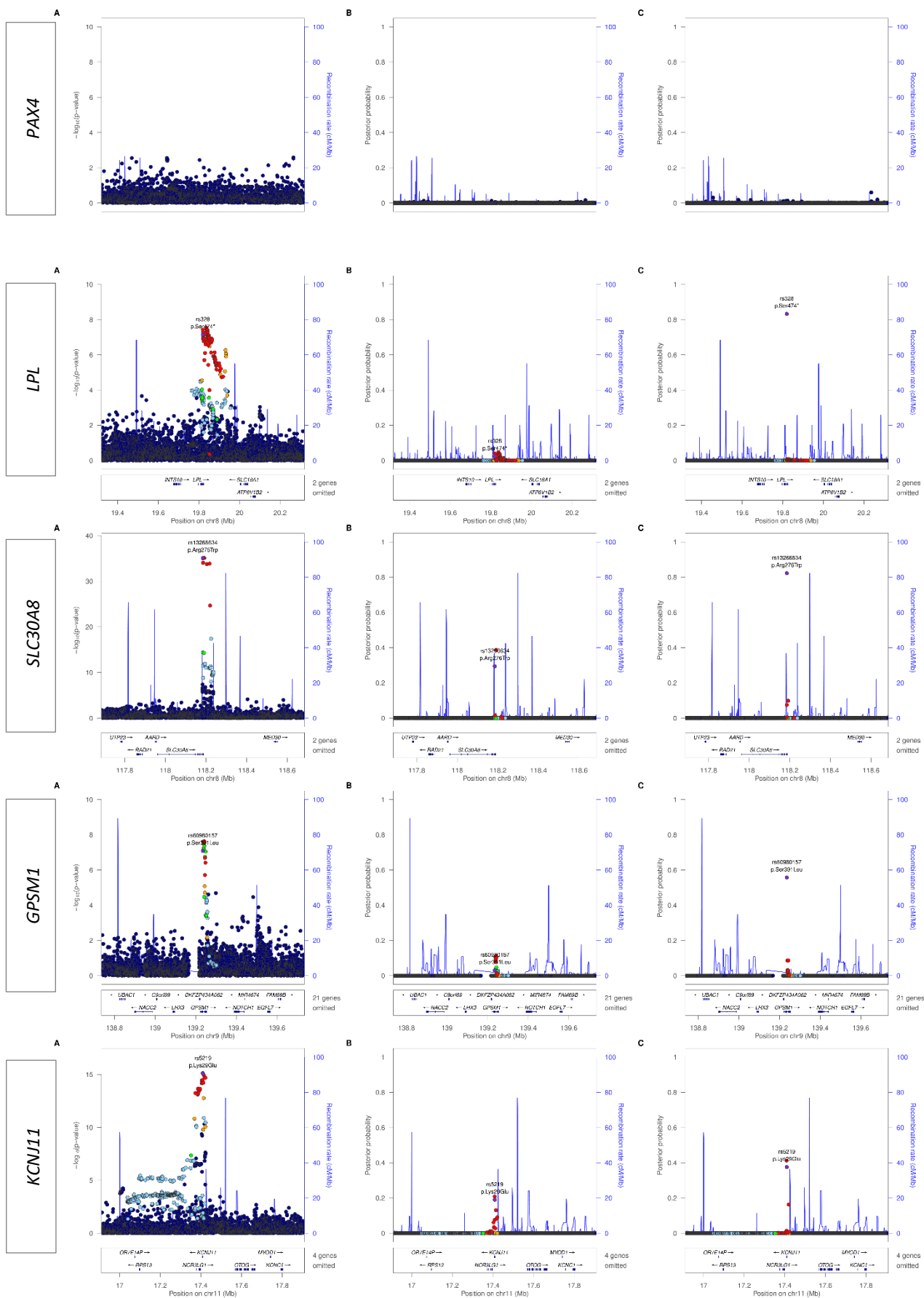


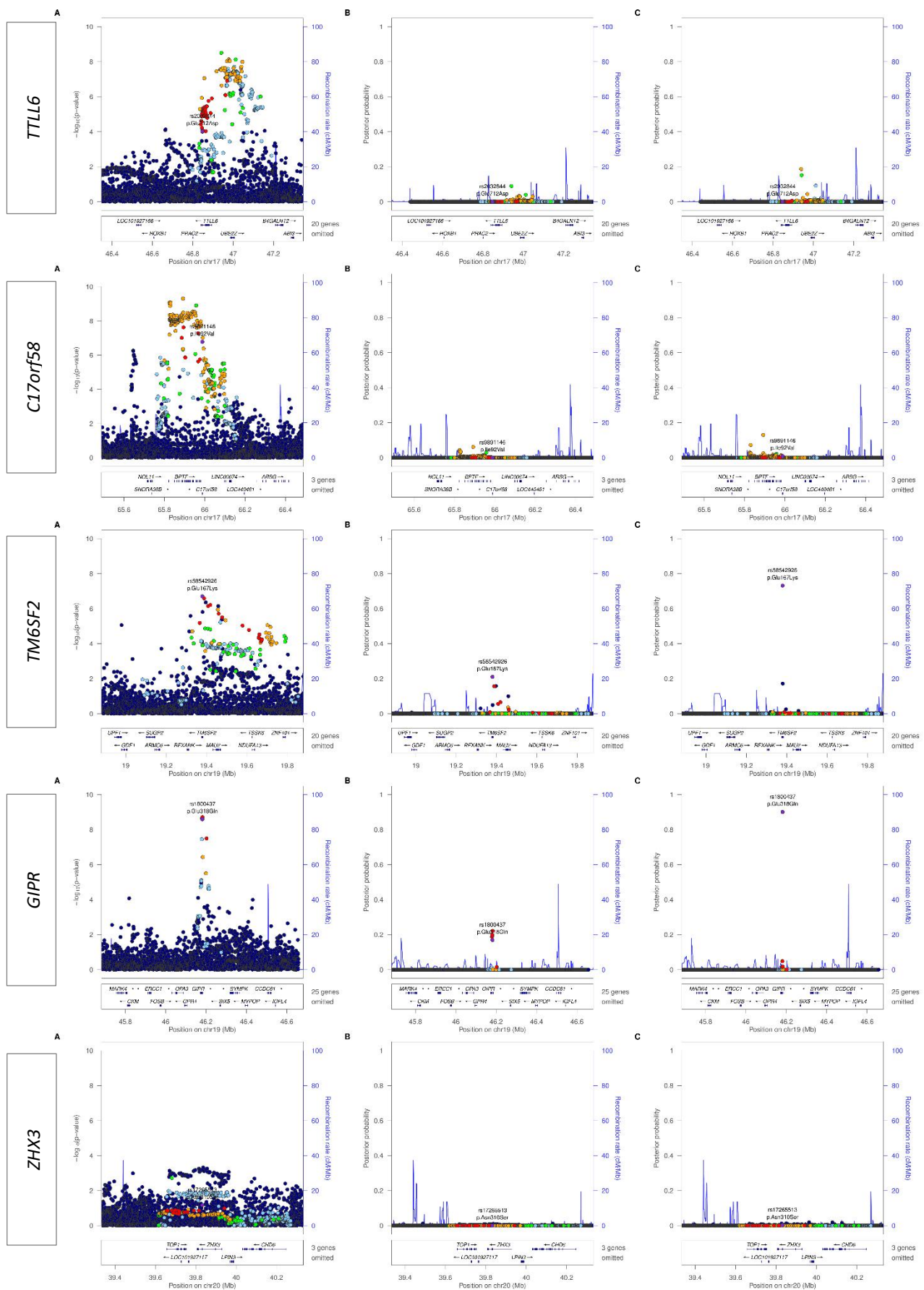
Supplementary Figure 5 | Locus zoom and posterior probability plots for the distinct association signals from fine-mapping analysis. For each locus: **a)** p -values for association from fine-mapping meta-analyses; **b)** posteriors for driving the association under functionally unweighted; and **c)** posteriors for driving the association under annotation informed priors. Each point represents a SNP passing quality control in the meta-analysis, plotted with their p -value (on a $-\log_{10}$ scale) or posteriors as a function of genomic position (NCBI build 37). In each plot, the index variant is represented by the purple symbol. The colour coding of all other SNPs indicates LD with the index variant in European ancestry haplotypes from the 1000 Genomes Project reference panel: red $r^2 \geq 0.8$; gold $0.6 \leq r^2 < 0.8$; green $0.4 \leq r^2 < 0.6$; cyan $0.2 \leq r^2 < 0.4$; blue $r^2 < 0.2$; grey r^2 unknown. Fine-mapping was performed using European ancestry GWAS meta-analysis including 50,160 T2D cases and 465,272 controls.







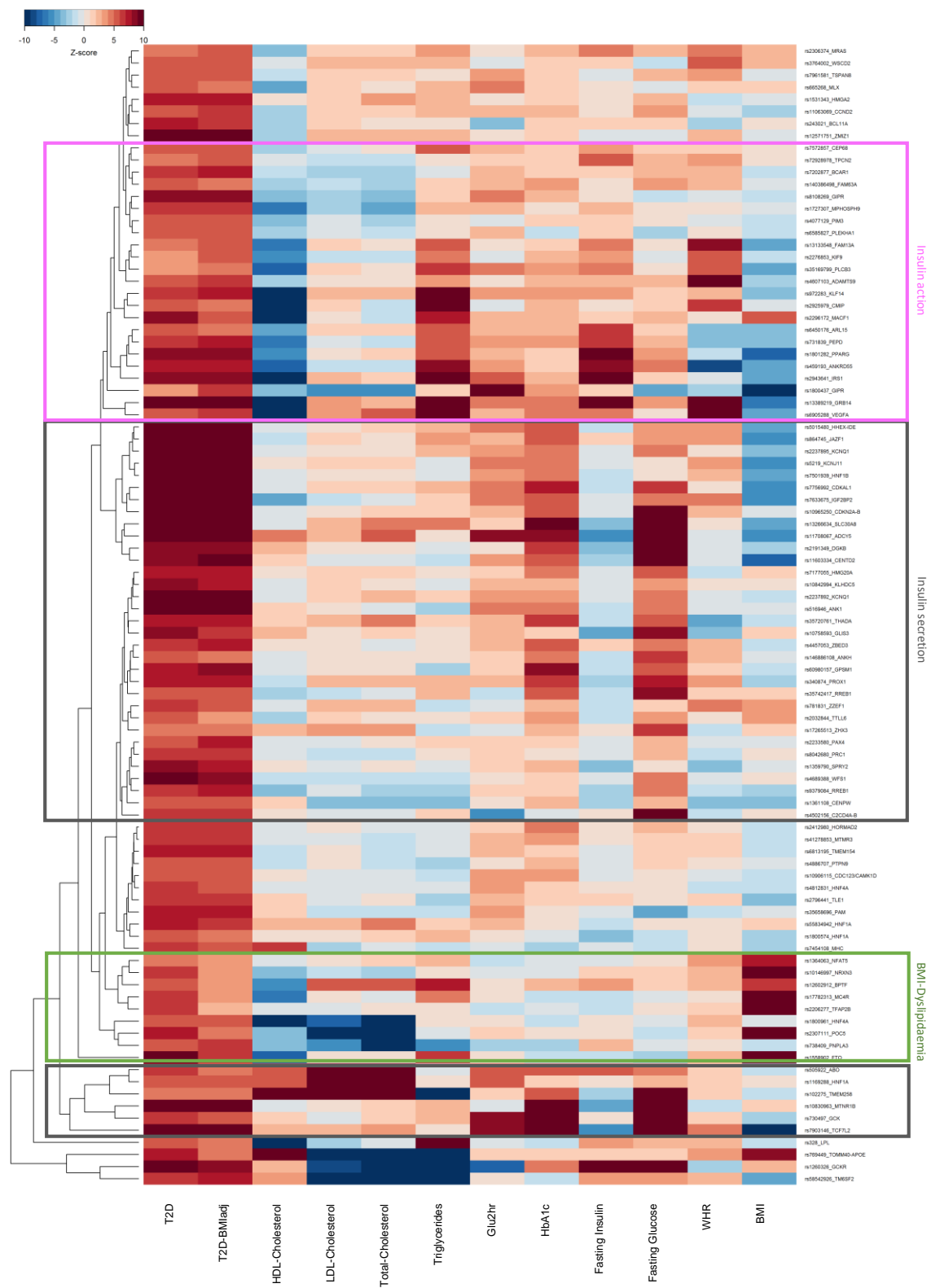




Supplementary Figure 6 | Clustering of type 2 diabetes loci based on similarity with glycemic, anthropometric traits, and lipid levels. a)

The Z-scores displayed in the heat map represent the effect of the lead T2D risk allele (y-axis) on the values of various metabolic and anthropometric traits (x-axis). Positive Z-scores in red indicate the T2D-risk allele increases the value of the trait concerned, and negative Z-scores in blue show that it is associated with a decrease in the trait value of interest. T2D loci (on y axis) are clustered by the complete agglomeration method and using the Euclidean distances of the Z-scores of the loci/traits, resulting in clustering of SNPs that are more significantly associated with the same set of traits. Z-scores are restricted to ± 10 . Insulin action: T2D risk allele showed higher fasting insulin levels adjusted for BMI, lower high-density lipoprotein cholesterol, and higher triglyceride levels. Insulin secretion: T2D risk allele demonstrated higher fasting glucose levels adjusted for BMI, higher 2-h glucose, higher glycated haemoglobin levels, and lower fasting insulin levels adjusted for BMI. HDL: high density lipoprotein. LDL: low density lipoprotein. Glu2hr: 2-h glucose. HbA1c: glycated haemoglobin. WHR: waist hip ratio. BMI: body mass index. **b)** Soft clustering performed using fuzzy c-means algorithm that assigns a score to a variant for each cluster. This allows each variant to be assigned to more than one cluster. Broadly variants can be assigned to six different clusters using this approach.

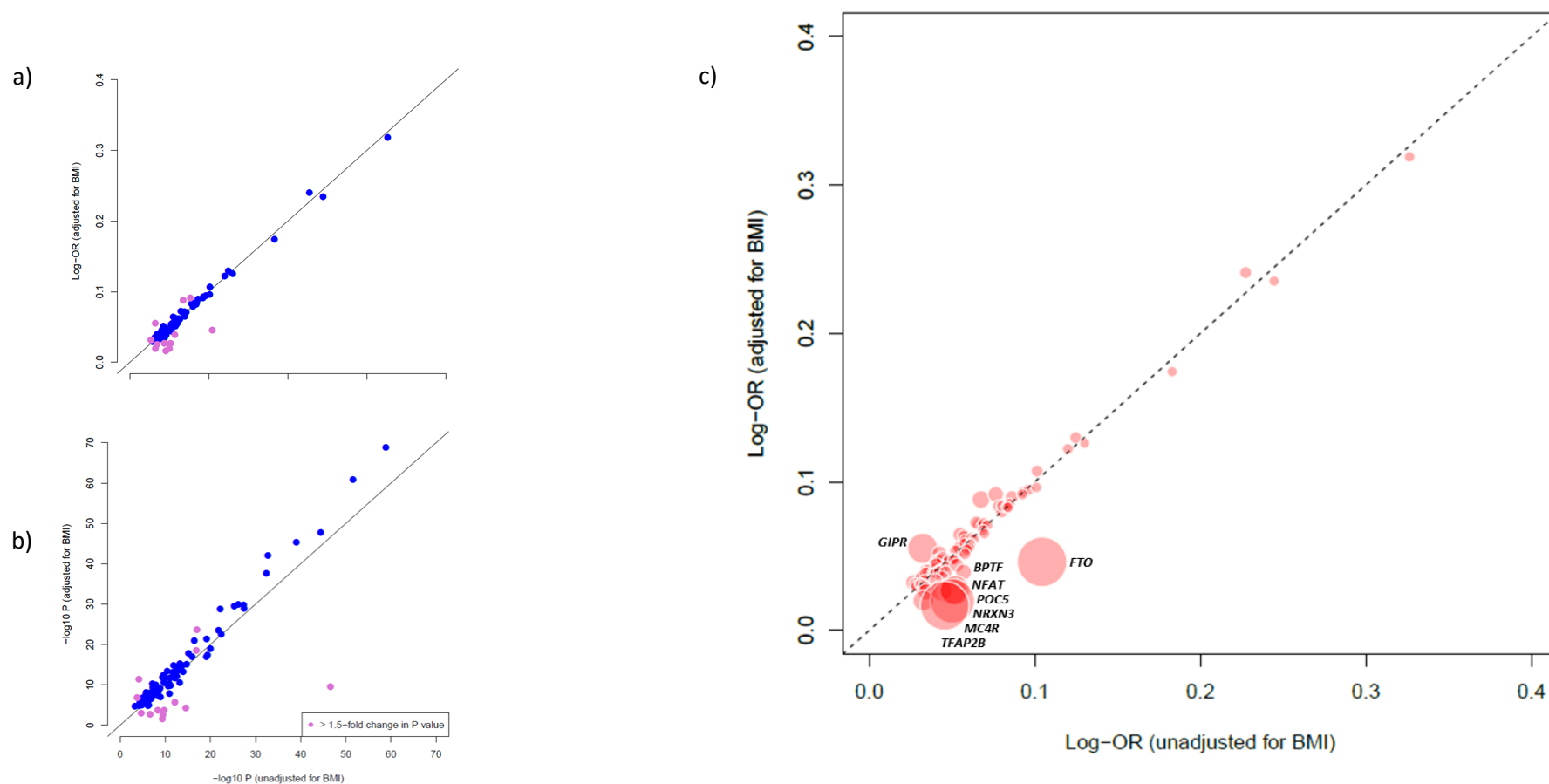
a)



b)



Supplementary Figure 7 | Comparison of estimated effect size and p -value between BMI-adjusted and unadjusted models. Plots comparing adjustment with BMI (x-axis) versus no adjustment for BMI (y-axis) from the trans-ethnic meta-analysis of 68,048 cases and 304,612 controls are shown for: **a)** odds ratio. Coding variants with >2 -fold change ($-\log_{10}P$ unadjusted/ $-\log_{10}P$ adjusted) are highlighted; and **b)** p -values for significant variant associations. Variants >1.5 -fold change in p -value are highlighted in pink. **c)** odds ratio; where the size of the circle varies with fold change in p -values: BMI-adjusted vs BMI-unadjusted.



ii. **Supplementary Tables**

Supplementary Tables 1 and 2 can be found in the Supplementary excel files.

Supplementary Table 1 | Study design, genotyping methods, quality control, and statistical analysis of studies genotyped using exome-array.

Supplementary Table 2 | Sample size and phenotype descriptives of studies genotyped using exome-array.

Supplementary Table 3 | Association summary statistics of coding variants attaining exome-wide significant ($p < 2.2 \times 10^{-7}$) evidence of association with T2D susceptibility in the discovery analysis.

(a) Trans-ethnic meta-analysis of 81,412 cases and 370,832.

Locus	Variant annotation	rs ID	Chr	Position	Alleles		RAF	BMI unadjusted			BMI adjusted		
					Risk	Other		OR (95% CI)	p-value	Cochran's Q p-value	OR (95% CI)	p-value	Cochran's Q p-value
MACF1	MACF1 p.Ile39Val	rs16826069	1	39,797,055	G	A	0.212	1.06 (1.04-1.07)	2.5×10^{-14}	0.36	1.05 (1.03-1.06)	7.0×10^{-9}	0.82
	MACF1 p.Lys1625Asn	rs41270807	1	39,801,815	C	A	0.199	1.07 (1.05-1.09)	2.5×10^{-15}	0.91	1.05 (1.03-1.07)	2.5×10^{-7}	0.95
	MACF1 p.Met1424Val	rs2296172	1	39,835,817	G	A	0.193	1.06 (1.05-1.08)	6.7×10^{-16}	0.84	1.04 (1.03-1.06)	5.9×10^{-8}	0.89
	MACF1 p.Ala3354Thr	rs587404	1	39,908,506	A	G	0.302	1.04 (1.02-1.05)	7.7×10^{-9}	0.30	1.03 (1.02-1.05)	2.3×10^{-6}	0.27
FAM63A	FAM63A p.Tyr95Asn	rs140386498	1	150,972,959	A	T	0.988	1.21 (1.14-1.28)	7.5×10^{-8}	0.29	1.19 (1.12-1.26)	6.7×10^{-7}	0.30
GCKR	GCKR p.Pro446Leu	rs1260326	2	27,730,940	C	T	0.630	1.06 (1.05-1.08)	5.3×10^{-25}	0.18	1.06 (1.04-1.07)	3.2×10^{-18}	0.44
	C2orf16 p.Ile774Val	rs1919128	2	27,801,759	A	G	0.735	1.04 (1.03-1.06)	9.9×10^{-11}	0.62	1.04 (1.02-1.05)	1.2×10^{-8}	0.77
	GPN1 p.Arg12Lys	rs3749147	2	27,851,918	G	A	0.763	1.04 (1.02-1.05)	2.1×10^{-8}	0.20	1.04 (1.02-1.05)	6.3×10^{-7}	0.36
THADA	THADA p.Cys845Tyr	rs35720761	2	43,519,977	C	T	0.895	1.08 (1.05-1.10)	4.6×10^{-15}	0.55	1.07 (1.05-1.10)	8.3×10^{-16}	0.59
	THADA p.Thr897Ala	rs7578597	2	43,732,823	T	C	0.898	1.06 (1.04-1.09)	2.7×10^{-9}	0.03	1.05 (1.03-1.08)	1.7×10^{-7}	0.024
CEP68	CEP68 p.Gly74Ser	rs7572857	2	65,296,798	G	A	0.846	1.05 (1.04-1.07)	8.3×10^{-9}	0.13	1.05 (1.03-1.07)	6.6×10^{-7}	0.13
GRB14	COBLL1 p.Asn901Asp	rs7607980	2	165,551,201	T	C	0.879	1.08 (1.06-1.11)	8.6×10^{-20}	0.14	1.09 (1.07-1.12)	5.0×10^{-23}	0.46
PPARG	PPARG p.Pro12Ala	rs1801282	3	12,393,125	C	G	0.887	1.09 (1.07-1.11)	1.4×10^{-17}	0.96	1.10 (1.07-1.12)	2.7×10^{-19}	0.93
KIF9-PTPN23	KIF9 p.Arg638Trp	rs2276853	3	47,282,303	A	G	0.588	1.02 (1.01-1.04)	8.0×10^{-5}	0.84	1.03 (1.02-1.05)	5.3×10^{-8}	0.87
	PTPN23 p.Ala818Thr	rs6780013	3	47,452,118	G	A	0.624	1.02 (1.01-1.04)	7.0×10^{-5}	0.693	1.03 (1.02-1.04)	3.6×10^{-7}	0.63
IGF2BP2	SEN2 p.Thr291Lys	rs6762208	3	185,331,165	A	C	0.367	1.03 (1.01-1.04)	1.6×10^{-6}	0.048	1.03 (1.02-1.05)	3.0×10^{-8}	0.058
WFS1	WFS1 p.Val333Ile	rs1801212	4	6,302,519	A	G	0.748	1.07 (1.06-1.09)	1.1×10^{-24}	0.13	1.07 (1.05-1.08)	7.1×10^{-21}	0.15
	WFS1 p.Arg611His	rs734312	4	6,303,354	A	G	0.542	1.06 (1.04-1.07)	2.0×10^{-18}	0.24	1.05 (1.03-1.06)	3.7×10^{-13}	0.39
ANKH	ANKH p.Arg187Gln	rs146886108	5	14,751,305	C	T	0.996	1.29 (1.16-1.45)	1.4×10^{-7}	0.58	1.27 (1.13-1.41)	3.5×10^{-7}	0.79
POC5	POC5 p.His36Arg	rs2307111	5	75,003,678	T	C	0.562	1.05 (1.04-1.07)	1.6×10^{-15}	0.85	1.03 (1.01-1.04)	2.1×10^{-5}	0.72
PAM-PPIP5K2	PAM p.Asp336Gly	rs35658696	5	102,338,811	G	A	0.0450	1.13 (1.10-1.17)	1.2×10^{-16}	0.34	1.13 (1.09-1.17)	7.4×10^{-15}	0.66
	PPIP5K2 p.Ser1207Gly	rs36046591	5	102,537,285	G	A	0.0450	1.13 (1.09-1.17)	1.4×10^{-16}	0.25	1.13 (1.09-1.16)	2.8×10^{-14}	0.52
RREB1	RREB1 p.Asp1171Asn	rs9379084	6	7,231,843	G	A	0.884	1.08 (1.06-1.11)	1.1×10^{-13}	0.75	1.10 (1.07-1.13)	1.5×10^{-17}	0.53
	RREB1 p.Ser1499Tyr	rs35742417	6	7,247,344	C	A	0.836	1.04 (1.03-1.06)	5.5×10^{-8}	0.31	1.04 (1.02-1.06)	2.2×10^{-7}	0.50
MHC	TCF19 p.Met131Val	rs2073721	6	31,129,616	G	A	0.749	1.04 (1.02-1.05)	1.6×10^{-10}	0.18	1.04 (1.02-1.05)	2.3×10^{-9}	0.36
	PRRC2A p.Leu1895Val	rs3132453	6	31,604,044	G	T	0.940	1.07 (1.05-1.10)	9.3×10^{-8}	0.67	1.06 (1.03-1.09)	4.9×10^{-6}	0.83
	SLC44A4 p.Met250Val	rs644827	6	31,838,441	C	T	0.559	1.03 (1.01-1.04)	1.6×10^{-5}	0.81	1.03 (1.02-1.05)	8.9×10^{-7}	0.80
	SLC44A4 p.Val183Ile	rs2242665	6	31,839,309	T	C	0.559	1.03 (1.01-1.04)	1.4×10^{-5}	0.85	1.03 (1.02-1.05)	7.1×10^{-7}	0.84
	EHMT2 p.Ser58Phe	rs115884658	6	31,864,538	A	G	0.0258	1.12 (1.08-1.17)	4.6×10^{-9}	0.059	1.13 (1.08-1.17)	4.2×10^{-7}	0.040
	PPT2 p.Cys5Trp	rs3134604	6	32,122,386	G	C	0.886	1.06 (1.04-1.08)	9.4×10^{-9}	0.086	1.05 (1.03-1.07)	4.6×10^{-7}	0.14
	BTNL2 p.Ser83Gly	rs2076530	6	32,363,816	C	T	0.421	1.03 (1.02-1.04)	3.5×10^{-5}	0.45	1.03 (1.02-1.05)	6.5×10^{-7}	0.52
	HLA-DQB1 p.Phe41Tyr	rs9274407	6	32,632,832	T	A	0.815	1.05 (1.03-1.07)	6.0×10^{-8}	0.26	1.04 (1.02-1.06)	5.4×10^{-5}	0.44
PAX4	PAX4 p.Arg190His	rs2233580	7	127,253,550	T	C	0.0294	1.36 (1.25-1.48)	1.8×10^{-12}	0.47	1.38 (1.26-1.51)	4.2×10^{-13}	0.50

<i>LPL</i>	<i>LPL</i> p.Ser474*	rs328	8	19,819,724	C	G	0.903	1.05 (1.03-1.08)	6.8x10 ⁻⁹	0.69	1.05 (1.03-1.07)	2.3x10 ⁻⁷	0.87
<i>SLC30A8</i>	<i>SLC30A8</i> p.Arg276Trp	rs13266634	8	118,184,783	C	T	0.691	1.09 (1.08-1.11)	1.9x10 ⁻⁴⁷	0.09	1.09 (1.08-1.11)	1.3x10 ⁻⁴⁷	0.041
<i>GPSM1</i>	<i>GPSM1</i> p.Ser391Leu	rs60980157	9	139,235,415	C	T	0.771	1.06 (1.05-1.08)	3.2x10 ⁻¹⁶	0.20	1.06 (1.05-1.08)	6.6x10 ⁻¹⁶	0.31
<i>KCNJ11-ABCC8</i>	<i>NUCB2</i> p.Gln338Glu	rs757081	11	17,351,683	G	C	0.320	1.04 (1.03-1.06)	8.6x10 ⁻⁹	0.54	1.05 (1.04-1.07)	5.6x10 ⁻¹¹	0.20
	<i>KCNJ11</i> p.Val250Ile	rs5215	11	17,408,630	C	T	0.365	1.06 (1.05-1.08)	4.5x10 ⁻²¹	0.66	1.07 (1.05-1.08)	3.2x10 ⁻²²	0.37
	<i>ABCC8</i> p.Lys29Glu	rs5219	11	17,409,572	T	C	0.364	1.06 (1.05-1.07)	5.7x10 ⁻²²	0.69	1.07 (1.05-1.08)	1.5x10 ⁻²²	0.37
	<i>ABCC8</i> p.Ala1369Ser	rs757110	11	17,418,477	C	A	0.367	1.06 (1.04-1.07)	8.1x10 ⁻¹⁹	0.66	1.06 (1.05-1.07)	5.4x10 ⁻¹⁹	0.33
<i>PLCB3</i>	<i>PLCB3</i> p.Ser778Leu	rs35169799	11	64,031,241	T	C	0.0585	1.04 (1.02-1.07)	0.00012	0.011	1.05 (1.03-1.08)	1.7x10 ⁻⁶	0.025
<i>TPCN2</i>	<i>TPCN2</i> p.Val219Ile	rs72928978	11	68,831,364	G	A	0.890	1.05 (1.02-1.07)	5.2x10 ⁻⁷	0.55	1.05 (1.03-1.07)	1.8x10 ⁻⁸	0.47
	<i>TPCN2</i> p.Met484Leu	rs35264875	11	68,846,399	A	T	0.847	1.05 (1.03-1.08)	4.5x10 ⁻⁵	0.24	1.07 (1.04-1.09)	9.6x10 ⁻⁸	0.20
<i>CENTD2</i>	<i>ARAP1</i> p.Gln802Glu	rs56200889	11	72,408,055	G	C	0.733	1.04 (1.02-1.05)	4.8x10 ⁻⁸	0.77	1.05 (1.03-1.06)	5.2x10 ⁻¹⁰	0.61
<i>KLHDC5</i>	<i>MRPS35</i> p.Gly43Arg	rs1127787	12	27,867,727	G	A	0.850	1.06 (1.04-1.08)	1.4x10 ⁻¹¹	0.72	1.05 (1.03-1.07)	1.5x10 ⁻⁸	0.85
	<i>MANSC4</i> p.Thr163Met	rs11049125	12	27,916,206	G	A	0.849	1.05 (1.04-1.07)	8.8x10 ⁻⁹	0.75	1.05 (1.03-1.06)	3.0x10 ⁻⁶	0.84
	<i>MANSC4</i> p.Leu157Ser	rs11049126	12	27,916,224	A	G	0.849	1.05 (1.04-1.07)	1.4x10 ⁻⁸	0.73	1.05 (1.03-1.06)	3.9x10 ⁻⁶	0.83
<i>WSCD2</i>	<i>WSCD2</i> p.Thr113Ile	rs3764002	12	108,618,630	C	T	0.719	1.03 (1.02-1.05)	3.3x10 ⁻⁸	0.076	1.03 (1.02-1.05)	1.2x10 ⁻⁷	0.28
<i>HNF1A</i>	<i>HNF1A</i> p.Ile75Leu	rs1169288	12	121,416,650	C	A	0.323	1.04 (1.03-1.06)	1.1x10 ⁻¹¹	0.00065	1.04 (1.02-1.06)	1.9x10 ⁻¹⁰	0.0023
	<i>HNF1A</i> p.Ala146Val	rs1800574	12	121,416,864	T	C	0.029	1.11 (1.06-1.15)	6.1x10 ⁻⁸	0.77	1.10 (1.06-1.15)	1.3x10 ⁻⁷	0.43
<i>MPHOSPH9</i>	<i>SBNO1</i> p.Ser729Asn	rs1060105	12	123,806,219	C	T	0.815	1.04 (1.02-1.06)	5.7x10 ⁻⁷	0.87	1.04 (1.02-1.06)	1.1x10 ⁻⁷	0.89
<i>ZZEF1</i>	<i>ZZEF1</i> p.Ile402Val	rs781831	17	3,947,644	C	T	0.422	1.04 (1.03-1.05)	8.3x10 ⁻¹¹	0.49	1.03 (1.02-1.05)	1.8x10 ⁻⁷	0.87
	<i>ZZEF1</i> p.Leu360Pro	rs781852	17	3,953,102	G	A	0.400	1.04 (1.03-1.06)	8.8x10 ⁻¹⁰	0.31	1.03 (1.02-1.05)	4.4x10 ⁻⁷	0.69
<i>MLX</i>	<i>MLX</i> p.Gln139Arg	rs665268	17	40,722,029	G	A	0.294	1.04 (1.02-1.05)	2.0x10 ⁻⁸	0.32	1.03 (1.02-1.04)	1.1x10 ⁻⁵	0.50
<i>TTLL6-CALCOCO2</i>	<i>TTLL6</i> p.Glu712Asp	rs2032844	17	46,847,364	C	A	0.754	1.04 (1.02-1.06)	1.2x10 ⁻⁷	0.33	1.03 (1.01-1.04)	0.00098	0.30
	<i>CALCOCO2</i> p.Pro347Ala	rs10278	17	46,939,658	C	G	0.710	1.04 (1.02-1.05)	4.7x10 ⁻⁷	0.72	1.03 (1.02-1.05)	3.0x10 ⁻⁵	0.59
<i>C17orf58</i>	<i>C17orf58</i> p.Ile92Val	rs9891146	17	65,988,049	T	C	0.332	1.04 (1.02-1.05)	7.2x10 ⁻⁷	0.20	1.02 (1.00-1.03)	0.0027	0.43
<i>CILP2</i>	<i>NCAN</i> p.Pro92Ser	rs2228603	19	19,329,924	T	C	0.0711	1.07 (1.05-1.10)	1.8x10 ⁻¹⁰	0.025	1.08 (1.05-1.11)	3.7x10 ⁻¹¹	0.027
	<i>TM6SF2</i> p.Glu167Lys	rs58542926	19	19,379,549	T	C	0.0755	1.07 (1.05-1.10)	4.8x10 ⁻¹²	0.099	1.09 (1.06-1.11)	3.4x10 ⁻¹⁵	0.089
	<i>ZNF101</i> Splice region	rs2304130	19	19,789,528	G	A	0.100	1.04 (1.02-1.06)	1.7x10 ⁻⁵	0.29	1.05 (1.03-1.07)	3.0x10 ⁻⁹	0.28
<i>GIPR</i>	<i>GIPR</i> p.Glu318Gln	rs1800437	19	46,181,392	C	G	0.200	1.03 (1.02-1.05)	7.1x10 ⁻⁵	0.96	1.06 (1.04-1.07)	6.8x10 ⁻¹²	0.93
<i>ZHX3</i>	<i>ZHX3</i> p.Asn310Ser	rs17265513	20	39,832,628	C	T	0.174	1.04 (1.02-1.06)	6.8x10 ⁻⁶	0.89	1.04 (1.02-1.05)	3.2x10 ⁻⁵	0.88
<i>HNF4A</i>	<i>HNF4A</i> p.Thr139Ile	rs1800961	20	43,042,364	T	C	0.0316	1.09 (1.05-1.13)	2.6x10 ⁻⁸	0.0005	1.10 (1.06-1.14)	5.0x10 ⁻⁸	0.0017
<i>MTMR3-ASCC2</i>	<i>ASCC2</i> p.Pro423Ser	rs36571	22	30,200,713	G	A	0.929	1.08 (1.06-1.11)	5.5x10 ⁻¹⁰	0.20	1.09 (1.06-1.11)	5.5x10 ⁻¹²	0.36
	<i>ASCC2</i> p.Asp407His	rs28265	22	30,200,761	C	G	0.925	1.09 (1.06-1.11)	2.1x10 ⁻¹²	0.12	1.09 (1.07-1.12)	4.4x10 ⁻¹⁴	0.34
	<i>ASCC2</i> p.Val123Ile	rs11549795	22	30,221,120	C	T	0.926	1.08 (1.06-1.11)	4.8x10 ⁻¹²	0.077	1.09 (1.06-1.12)	1.5x10 ⁻¹³	0.21
	<i>MTMR3</i> p.Asn960Ser	rs41278853	22	30,416,527	A	G	0.926	1.09 (1.06-1.11)	5.6x10 ⁻¹³	0.064	1.09 (1.06-1.12)	5.0x10 ⁻¹⁴	0.21
<i>PNPLA3</i>	<i>PNPLA3</i> p.Ile148Met	rs738409	22	44,324,727	G	C	0.239	1.04 (1.03-1.05)	2.1x10 ⁻¹⁰	0.98	1.05 (1.03-1.06)	2.8x10 ⁻¹¹	0.99
<i>PIM3</i>	<i>PIM3</i> p.Val300Ala	rs4077129	22	50,356,693	T	C	0.276	1.04 (1.02-1.05)	1.9x10 ⁻⁷	0.79	1.04 (1.02-1.06)	3.5x10 ⁻⁸	0.51

(b) European-specific meta-analysis of 48,286 cases and 250,671 controls.

Locus	Variant annotation	rs ID	Chr	Position	Alleles		RAF	BMI unadjusted			BMI adjusted		
					Risk	Other		OR (95% CI)	p-value	Cochran's Q p-value	OR (95% CI)	p-value	Cochran's Q p-value
MACF1	MACF1 p.Ile39Val	rs16826069	1	39,797,055	G	A	0.221	1.06 (1.04-1.08)	8.9x10 ⁻¹¹	0.82	1.05 (1.03-1.07)	8.8x10 ⁻⁹	0.91
	MACF1 p.Lys1625Asn	rs41270807	1	39,801,815	C	A	0.217	1.06 (1.04-1.08)	4.4x10 ⁻¹⁰	0.89	1.05 (1.03-1.07)	7.4x10 ⁻⁸	0.93
	MACF1 p.Met1424Val	rs2296172	1	39,835,817	G	A	0.217	1.06 (1.04-1.08)	1.2x10 ⁻¹⁰	0.87	1.05 (1.03-1.07)	1.2x10 ⁻⁸	0.93
	MACF1 p.Ala3354Thr	rs587404	1	39,908,506	A	G	0.296	1.04 (1.02-1.06)	1.7x10 ⁻⁷	0.63	1.04 (1.02-1.05)	7.3x10 ⁻⁸	0.79
FAM63A	FAM63A p.Tyr95Asn	rs140386498	1	150,972,959	A	T	0.986	1.22 (1.14-1.30)	5.8x10 ⁻⁸	0.43	1.20 (1.13-1.28)	5.9x10 ⁻⁸	0.43
GCKR	GCKR p.Pro446Leu	rs1260326	2	27,730,940	C	T	0.617	1.06 (1.04-1.07)	1.0x10 ⁻¹⁵	0.088	1.05 (1.04-1.07)	9.9x10 ⁻¹⁵	0.44
	C2orf16 p.Ile774Val	rs1919128	2	27,801,759	A	G	0.743	1.04 (1.02-1.05)	2.1x10 ⁻⁶	0.43	1.03 (1.02-1.05)	4.5x10 ⁻⁶	0.66
	GPN1 p.Arg12Lys	rs3749147	2	27,851,918	G	A	0.752	1.04 (1.02-1.06)	6.9x10 ⁻⁶	0.15	1.03 (1.02-1.05)	2.0x10 ⁻⁵	0.32
THADA	THADA p.Cys845Tyr	rs35720761	2	43,519,977	C	T	0.889	1.08 (1.05-1.10)	1.1x10 ⁻¹²	0.38	1.08 (1.06-1.10)	9.9x10 ⁻¹⁵	0.47
	THADA p.Thr897Ala	rs7578597	2	43,732,823	T	C	0.909	1.07 (1.04-1.11)	3.0x10 ⁻⁹	0.42	1.08 (1.05-1.11)	1.6x10 ⁻¹⁰	0.46
CEP68	CEP68 p.Gly74Ser	rs7572857	2	65,296,798	G	A	0.833	1.05 (1.03-1.07)	7.9x10 ⁻⁶	0.18	1.05 (1.03-1.07)	6.0x10 ⁻⁶	0.18
GRB14	COBL1 p.Asn901Asp	rs7607980	2	165,551,201	T	C	0.881	1.09 (1.06-1.11)	5.0x10 ⁻¹⁵	0.061	1.09 (1.07-1.12)	6.5x10 ⁻¹⁹	0.31
PPARG	PPARG p.Pro12Ala	rs1801282	3	12,393,125	C	G	0.871	1.08 (1.05-1.10)	4.8x10 ⁻¹²	0.88	1.09 (1.07-1.12)	1.0x10 ⁻¹⁶	0.83
KIF9-PTPN23	KIF9 p.Arg638Trp	rs2276853	3	47,282,303	A	G	0.599	1.03 (1.01-1.04)	8.4x10 ⁻⁵	0.40	1.03 (1.02-1.05)	6.7x10 ⁻⁷	0.59
	PTPN23 p.Ala818Thr	rs6780013	3	47,452,118	G	A	0.616	1.03 (1.01-1.04)	2.5x10 ⁻⁵	0.78	1.03 (1.02-1.05)	2.0x10 ⁻⁷	0.79
IGF2BP2	SEN2 p.Thr291Lys	rs6762208	3	185,331,165	A	C	0.338	1.03 (1.01-1.04)	6.7x10 ⁻⁵	0.26	1.03 (1.02-1.05)	9.6x10 ⁻⁶	0.25
WFS1	WFS1 p.Val333Ile	rs1801212	4	6,302,519	A	G	0.710	1.07 (1.05-1.09)	6.7x10 ⁻²⁰	0.16	1.06 (1.05-1.08)	2.1x10 ⁻¹⁷	0.13
	WFS1 p.Arg611His	rs734312	4	6,303,354	A	G	0.532	1.05 (1.04-1.07)	5.6x10 ⁻¹³	0.47	1.05 (1.03-1.06)	7.9x10 ⁻¹²	0.65
ANKH	ANKH p.Arg187Gln	rs146886108	5	14,751,305	C	T	0.995	1.29 (1.15-1.45)	2.0x10 ⁻⁷	0.16	1.28 (1.14-1.43)	1.1x10 ⁻⁷	0.32
POC5	POC5 p.His36Arg	rs2307111	5	75,003,678	T	C	0.597	1.06 (1.04-1.07)	4.8x10 ⁻¹²	0.30	1.03 (1.02-1.05)	2.6x10 ⁻⁶	0.55
PAM-PPIP5K2	PAM p.Asp336Gly	rs35658696	5	102,338,811	G	A	0.051	1.13 (1.09-1.17)	5.9x10 ⁻¹²	0.55	1.13 (1.09-1.17)	3.5x10 ⁻¹³	0.77
	PPIP5K2 p.Ser1207Gly	rs36046591	5	102,537,285	G	A	0.051	1.12 (1.08-1.16)	1.3x10 ⁻¹¹	0.52	1.12 (1.09-1.16)	1.1x10 ⁻¹²	0.74
RREB1	RREB1 p.Asp1171Asn	rs9379084	6	7,231,843	G	A	0.887	1.10 (1.07-1.13)	1.6x10 ⁻¹²	0.98	1.09 (1.06-1.12)	1.8x10 ⁻¹³	0.94
	RREB1 p.Ser1499Tyr	rs35742417	6	7,247,344	C	A	0.807	1.04 (1.02-1.06)	5.8x10 ⁻⁶	0.47	1.04 (1.02-1.06)	3.1x10 ⁻⁶	0.64
MHC	TCF19 p.Met131Val	rs2073721	6	31,129,616	G	A	0.742	1.04 (1.02-1.06)	5.6x10 ⁻⁹	0.039	1.04 (1.03-1.06)	6.1x10 ⁻¹⁰	0.16
	PRRC2A p.Leu1895Val	rs3132453	6	31,604,044	G	T	0.926	1.07 (1.04-1.10)	3.0x10 ⁻⁷	0.56	1.06 (1.03-1.09)	1.0x10 ⁻⁵	0.75
	SLC44A4 p.Met250Val	rs644827	6	31,838,441	C	T	0.535	1.03 (1.02-1.05)	3.0x10 ⁻⁶	0.74	1.04 (1.02-1.05)	1.8x10 ⁻⁷	0.64
	SLC44A4 p.Val183Ile	rs2242665	6	31,839,309	T	C	0.535	1.03 (1.02-1.05)	1.9x10 ⁻⁶	0.79	1.04 (1.02-1.05)	1.0x10 ⁻⁷	0.704
	EHMT2 p.Ser58Phe	rs115884658	6	31,864,538	A	G	0.031	1.10 (1.05-1.15)	5.3x10 ⁻⁶	0.13	1.13 (1.08-1.18)	4.1x10 ⁻⁹	0.088
	PPT2 p.Cys5Trp	rs3134604	6	32,122,386	G	C	0.868	1.06 (1.04-1.09)	1.7x10 ⁻⁸	0.15	1.06 (1.03-1.08)	1.2x10 ⁻⁷	0.18
	BTNL2 p.Ser83Gly	rs2076530	6	32,363,816	C	T	0.434	1.03 (1.02-1.05)	3.8x10 ⁻⁶	0.30	1.04 (1.03-1.05)	3.9x10 ⁻⁹	0.48
	HLA-DQB1 p.Phe41Tyr	rs9274407	6	32,632,832	T	A	0.818	1.04 (1.02-1.07)	6.2x10 ⁻⁵	0.093	1.04 (1.02-1.06)	9.2x10 ⁻⁵	0.18
PAX4	PAX4 p.Arg190His	rs2233580	7	127,253,550	T	C	N/A	N/A	N/A	N/A	N/A	N/A	N/A
LPL	LPL p.Ser474*	rs328	8	19,819,724	C	G	0.902	1.05 (1.03-1.08)	3.0x10 ⁻⁶	0.82	1.05 (1.03-1.07)	2.6x10 ⁻⁶	0.95
SLC30A8	SLC30A8 p.Arg276Trp	rs13266634	8	118,184,783	C	T	0.680	1.09 (1.07-1.10)	5.5x10 ⁻³⁰	0.12	1.09 (1.07-1.11)	7.7x10 ⁻³⁶	0.045
GPSM1	GPSM1 p.Ser391Leu	rs60980157	9	139,235,415	C	T	0.747	1.07 (1.05-1.09)	4.8x10 ⁻¹⁵	0.21	1.07 (1.05-1.08)	2.0x10 ⁻¹⁵	0.34
	NUCB2 p.Gln338Glu	rs757081	11	17,351,683	G	C	0.340	1.05 (1.03-1.07)	1.4x10 ⁻⁸	0.27	1.06 (1.04-1.08)	2.9x10 ⁻¹²	0.13

KCNJ11-ABCC8	KCNJ11 p.Val250Ile	rs5215	11	17,408,630	C	T	0.389	1.06 (1.05-1.08)	3.8x10 ⁻¹⁷	0.91	1.07 (1.05-1.08)	4.6x10 ⁻²²	0.72
	KCNJ11 p.Lys29Glu	rs5219	11	17,409,572	T	C	0.389	1.06 (1.05-1.08)	4.8x10 ⁻¹⁷	0.91	1.07 (1.05-1.08)	6.6x10 ⁻²²	0.73
	ABCC8 p.Ala1369Ser	rs757110	11	17,418,477	C	A	0.390	1.06 (1.04-1.07)	4.9x10 ⁻¹⁵	0.88	1.06 (1.05-1.08)	2.1x10 ⁻¹⁹	0.72
PLCB3	PLCB3 p.Ser778Leu	rs35169799	11	64,031,241	T	C	0.071	1.05 (1.02-1.08)	1.3x10 ⁻⁵	0.067	1.06 (1.03-1.09)	1.8x10 ⁻⁷	0.17
TPCN2	TPCN2 p.Val219Ile	rs72928978	11	68,831,364	G	A	0.857	1.05 (1.02-1.07)	6.7x10 ⁻⁶	0.17	1.05 (1.02-1.07)	5.1x10 ⁻⁶	0.13
	TPCN2 p.Met484Leu	rs35264875	11	68,846,399	A	T	0.827	1.07 (1.04-1.09)	1.6x10 ⁻⁶	0.14	1.06 (1.04-1.09)	2.2x10 ⁻⁶	0.18
CENTD2	ARAP1 p.Gln802Glu	rs56200889	11	72,408,055	G	C	0.721	1.04 (1.02-1.06)	1.5x10 ⁻⁵	0.63	1.05 (1.04-1.07)	2.1x10 ⁻⁹	0.44
KLHDC5	MRPS35 p.Gly43Arg	rs1127787	12	27,867,727	G	A	0.840	1.06 (1.04-1.08)	1.6x10 ⁻⁹	0.49	1.05 (1.03-1.07)	2.6x10 ⁻⁸	0.67
	MANSC4 p.Thr163Met	rs11049125	12	27,916,206	G	A	0.842	1.06 (1.04-1.08)	1.4x10 ⁻⁷	0.68	1.05 (1.03-1.07)	7.8x10 ⁻⁷	0.77
	MANSC4 p.Leu157Ser	rs11049126	12	27,916,224	A	G	0.842	1.06 (1.03-1.08)	1.8x10 ⁻⁷	0.64	1.05 (1.03-1.07)	9.6x10 ⁻⁷	0.75
WSCD2	WSCD2 p.Thr113Ile	rs3764002	12	108,618,630	C	T	0.726	1.04 (1.02-1.05)	8.7x10 ⁻⁸	0.023	1.04 (1.02-1.05)	6.3x10 ⁻⁸	0.14
HNF1A	HNF1A p.Ile75Leu	rs1169288	12	121,416,650	C	A	0.337	1.04 (1.02-1.06)	1.6x10 ⁻⁷	0.00051	1.04 (1.02-1.05)	1.4x10 ⁻⁷	0.0040
	HNF1A p.Ala146Val	rs1800574	12	121,416,864	T	C	0.033	1.11 (1.06-1.16)	3.9x10 ⁻⁷	0.92	1.10 (1.06-1.15)	1.7x10 ⁻⁷	0.54
MPHOSPH9	SBNO1 p.Ser729Asn	rs1060105	12	123,806,219	C	T	0.796	1.04 (1.02-1.06)	1.1x10 ⁻⁵	0.72	1.04 (1.02-1.06)	3.5x10 ⁻⁶	0.76
ZZEF1	ZZEF1 p.Ile402Val	rs781831	17	3,947,644	C	T	0.403	1.05 (1.03-1.06)	3.8x10 ⁻⁹	0.43	1.04 (1.02-1.05)	2.0x10 ⁻⁷	0.87
	ZZEF1 p.Leu360Pro	rs781852	17	3,953,102	G	A	0.387	1.05 (1.03-1.07)	9.1x10 ⁻¹¹	0.57	1.04 (1.03-1.06)	7.6x10 ⁻⁹	0.90
MLX	MLX p.Gln139Arg	rs665268	17	40,722,029	G	A	0.272	1.03 (1.01-1.05)	6.1x10 ⁻⁵	0.73	1.03 (1.01-1.04)	0.00053	0.92
TTLL6-CALCOCO2	TTLL6 p.Glu712Asp	rs2032844	17	46,847,364	C	A	0.754	1.04 (1.02-1.06)	4.4x10 ⁻⁶	0.61	1.03 (1.01-1.05)	0.00025	0.58
	CALCOCO2 p.Pro347Ala	rs10278	17	46,939,658	C	G	0.706	1.05 (1.03-1.06)	3.1x10 ⁻⁸	0.91	1.04 (1.02-1.05)	2.6x10 ⁻⁶	0.74
C17orf58	C17orf58 p.Ile92Val	rs9891146	17	65,988,049	T	C	0.277	1.04 (1.02-1.06)	1.3x10 ⁻⁷	0.32	1.02 (1.00-1.04)	0.00058	0.44
CILP2	NCAN p.Pro92Ser	rs2228603	19	19,329,924	T	C	0.078	1.07 (1.04-1.10)	3.5x10 ⁻⁷	0.15	1.08 (1.05-1.11)	2.0x10 ⁻⁹	0.23
	TM6SF2 p.Glu167Lys	rs58542926	19	19,379,549	T	C	0.079	1.09 (1.06-1.12)	1.7x10 ⁻¹⁰	0.71	1.09 (1.06-1.12)	1.3x10 ⁻¹²	0.75
	ZNF101 Splice region	rs2304130	19	19,789,528	G	A	0.084	1.07 (1.04-1.10)	6.5x10 ⁻⁸	0.36	1.08 (1.05-1.11)	3.1x10 ⁻¹¹	0.55
GIPR	GIPR p.Glu318Gln	rs1800437	19	46,181,392	C	G	0.218	1.03 (1.02-1.05)	0.00021	0.84	1.06 (1.04-1.08)	3.1x10 ⁻¹²	0.84
ZHX3	ZHX3 p.Asn310Ser	rs17265513	20	39,832,628	C	T	0.211	1.05 (1.03-1.07)	9.2x10 ⁻⁸	0.86	1.04 (1.02-1.05)	2.9x10 ⁻⁶	0.78
HNF4A	HNF4A p.Thr139Ile	rs1800961	20	43,042,364	T	C	0.035	1.09 (1.04-1.13)	3.1x10 ⁻⁶	0.00082	1.09 (1.05-1.13)	6.5x10 ⁻⁷	0.0018
MTMR3-ASCC2	ASCC2 p.Pro423Ser	rs36571	22	30,200,713	G	A	0.917	1.09 (1.06-1.12)	3.0x10 ⁻¹⁰	0.11	1.09 (1.06-1.12)	7.7x10 ⁻¹²	0.42
	ASCC2 p.Asp407His	rs28265	22	30,200,761	C	G	0.916	1.09 (1.06-1.12)	5.2x10 ⁻¹¹	0.15	1.09 (1.06-1.12)	1.2x10 ⁻¹²	0.54
	ASCC2 p.Val123Ile	rs11549795	22	30,221,120	C	T	0.916	1.09 (1.06-1.12)	2.3x10 ⁻¹⁰	0.10	1.09 (1.06-1.12)	4.3x10 ⁻¹²	0.42
	MTMR3 p.Asn960Ser	rs41278853	22	30,416,527	A	G	0.917	1.09 (1.06-1.12)	4.0x10 ⁻¹¹	0.075	1.09 (1.06-1.12)	1.7x10 ⁻¹²	0.31
PNPLA3	PNPLA3 p.Ile148Met	rs738409	22	44,324,727	G	C	0.227	1.04 (1.02-1.06)	8.1x10 ⁻⁷	0.93	1.04 (1.03-1.06)	3.0x10 ⁻⁸	0.96
PIM3	PIM3 p.Val300Ala	rs4077129	22	50,356,693	T	C	0.259	1.04 (1.02-1.06)	7.0x10 ⁻⁶	0.84	1.04 (1.02-1.05)	1.1x10 ⁻⁵	0.49

Chr: chromosome. RAF: risk allele frequency. BMI: body mass index. OR: odds ratio. CI: confidence interval.

Supplementary Table 4 | Summary statistics for additive, recessive and dominant models for coding variants attaining exome-wide significant evidence ($p < 2.2 \times 10^{-7}$) of association with T2D susceptibility in the discovery analysis.

(a) Trans-ethnic meta-analysis of 58,425 cases and 188,032 controls.

(i) BMI unadjusted analyses.

Locus	Variant annotation	rs ID	Chr	Position	Alleles		RAF	Additive		Recessive		Dominant	
					Risk	Other		OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
MACF1	MACF1 p.Ile39Val	rs16826069	1	39,797,055	G	A	0.210	1.05 (1.03-1.07)	8.8×10^{-10}	1.12 (1.07-1.17)	1.6×10^{-7}	1.05 (1.03-1.07)	2.2×10^{-7}
	MACF1 p.Lys1625Asn	rs41270807	1	39,801,815	C	A	0.195	1.06 (1.04-1.08)	1.2×10^{-9}	1.14 (1.08-1.20)	7.4×10^{-7}	1.06 (1.04-1.08)	2.2×10^{-7}
	MACF1 p.Met1424Val	rs2296172	1	39,835,817	G	A	0.187	1.05 (1.04-1.07)	1.4×10^{-10}	1.14 (1.08-1.19)	5.2×10^{-8}	1.05 (1.03-1.07)	7.3×10^{-8}
	MACF1 p.Ala3354Thr	rs587404	1	39,908,506	A	G	0.301	1.03 (1.01-1.04)	1.3×10^{-5}	1.04 (1.02-1.06)	5.3×10^{-5}	1.04 (1.01-1.07)	0.0032
FAM63A	FAM63A p.Tyr95Asn	rs140386498	1	150,972,959	A	T	0.988	1.23 (1.15-1.32)	1.2×10^{-6}	1.45 (0.69-3.06)	0.76	1.23 (1.15-1.32)	6.7×10^{-7}
GCKR	GCKR p.Pro446Leu	rs1260326	2	27,730,940	C	T	0.642	1.06 (1.04-1.07)	8.8×10^{-17}	1.08 (1.05-1.10)	1.0×10^{-13}	1.08 (1.05-1.11)	1.5×10^{-9}
	C2orf16 p.Ile774Val	rs1919128	2	27,801,759	A	G	0.74	1.04 (1.02-1.06)	1.0×10^{-8}	1.05 (1.02-1.09)	0.00064	1.05 (1.03-1.07)	4.2×10^{-8}
	GPN1 p.Arg12Lys	rs3749147	2	27,851,918	G	A	0.771	1.04 (1.02-1.05)	6.7×10^{-7}	1.04 (1.02-1.06)	1.2×10^{-5}	1.06 (1.02-1.11)	0.00024
THADA	THADA p.Cys845Tyr	rs35720761	2	43,519,977	C	T	0.9	1.07 (1.04-1.09)	7.6×10^{-10}	1.07 (1.05-1.10)	1.9×10^{-10}	1.06 (0.97-1.17)	0.2
	THADA p.Thr897Ala	rs7578597	2	43,732,823	T	C	0.9	1.05 (1.02-1.07)	0.00011	1.05 (0.95-1.15)	0.18	1.05 (1.02-1.08)	0.00011
CEP68	CEP68 p.Gly74Ser	rs7572857	2	65,296,798	G	A	0.849	1.05 (1.03-1.07)	2.4×10^{-6}	1.06 (1.03-1.08)	4.3×10^{-6}	1.09 (1.03-1.17)	0.023
GRB14	COBLL1 p.Asn901Asp	rs7607980	2	165,551,201	T	C	0.878	1.08 (1.06-1.11)	5.7×10^{-13}	1.13 (1.04-1.23)	0.0036	1.09 (1.07-1.12)	7.5×10^{-13}
PPARG	PPARG p.Pro12Ala	rs1801282	3	12,393,125	C	G	0.888	1.07 (1.05-1.10)	4.3×10^{-10}	1.17 (1.07-1.28)	0.00017	1.08 (1.05-1.10)	3.0×10^{-9}
KIF9-PTPN23	KIF9 p.Arg638Trp	rs2276853	3	47,282,303	A	G	0.587	1.02 (1.01-1.04)	0.0007	1.04 (1.02-1.06)	8.9×10^{-5}	1.01 (0.99-1.04)	0.18
	PTPN23 p.Ala818Thr	rs6780013	3	47,452,118	G	A	0.628	1.02 (1.01-1.04)	0.0013	1.03 (1.01-1.06)	0.00082	1.02 (0.99-1.05)	0.13
IGF2BP2	SEN2 p.Thr291Lys	rs6762208	3	185,331,165	A	C	0.374	1.03 (1.02-1.05)	2.3×10^{-6}	1.04 (1.02-1.06)	3.0×10^{-5}	1.05 (1.02-1.08)	0.001
WFS1	WFS1 p.Val333Ile	rs1801212	4	6,302,519	A	G	0.753	1.07 (1.05-1.09)	2.0×10^{-18}	1.08 (1.06-1.11)	3.5×10^{-16}	1.12 (1.07-1.16)	6.8×10^{-8}
	WFS1 p.Arg611His	rs734312	4	6,303,354	A	G	0.543	1.05 (1.04-1.07)	1.7×10^{-11}	1.06 (1.03-1.08)	1.5×10^{-6}	1.08 (1.06-1.11)	3.2×10^{-9}
ANKH	ANKH p.Arg187Gln	rs146886108	5	14,751,305	C	T	0.996	1.20 (1.06-1.36)	0.0018	1.20 (1.06-1.35)	0.0019	3.22 (0.48-21.66)	0.24
POC5	POC5 p.His36Arg	rs2307111	5	75,003,678	T	C	0.551	1.04 (1.03-1.06)	4.7×10^{-8}	1.05 (1.02-1.08)	4.2×10^{-5}	1.06 (1.03-1.08)	9.9×10^{-7}
PAM-PP1P5K2	PAM p.Asp336Gly	rs35658696	5	102,338,811	G	A	0.044	1.12 (1.07-1.16)	5.7×10^{-9}	1.36 (1.07-1.72)	0.0039	1.12 (1.07-1.16)	1.4×10^{-8}
	PP1P5K2 p.Ser1207Gly	rs36046591	5	102,537,285	G	A	0.045	1.12 (1.08-1.16)	5.0×10^{-10}	1.47 (1.18-1.83)	0.00035	1.12 (1.08-1.16)	2.8×10^{-9}
RREB1	RREB1 p.Asp1171Asn	rs9379084	6	7,231,843	G	A	0.889	1.09 (1.06-1.12)	9.1×10^{-10}	1.10 (1.07-1.14)	4.9×10^{-10}	1.12 (1.00-1.24)	0.063
	RREB1 p.Ser1499Tyr	rs35742417	6	7,247,344	C	A	0.837	1.04 (1.02-1.06)	1.7×10^{-6}	1.05 (1.03-1.07)	5.2×10^{-7}	1.04 (0.98-1.09)	0.14
MHC	TCF19 p.Met131Val	rs2073721	6	31,129,616	G	A	0.747	1.03 (1.02-1.05)	1.6×10^{-5}	1.03 (1.01-1.05)	0.00021	1.07 (1.03-1.11)	0.00041
	PRRC2A p.Leu1895Val	rs3132453	6	31,604,044	G	T	0.943	1.07 (1.03-1.10)	2.3×10^{-5}	1.07 (1.04-1.11)	1.0×10^{-5}	1.05 (0.90-1.23)	0.59
	SLC44A4 p.Met250Val	rs644827	6	31,838,441	C	T	0.558	1.02 (1.01-1.04)	0.00043	1.03 (1.01-1.05)	0.0062	1.04 (1.01-1.07)	0.002
	SLC44A4 p.Val183Ile	rs2242665	6	31,839,309	T	C	0.558	1.02 (1.01-1.04)	0.00036	1.03 (1.01-1.05)	0.0072	1.04 (1.01-1.07)	0.0012
	EHMT2 p.Ser58Phe	rs115884658	6	31,864,538	A	G	0.029	1.10 (1.05-1.15)	0.00081	1.10 (1.05-1.15)	0.00079	1.33 (0.98-1.81)	0.27
	PPT2 p.Cys5Trp	rs3134604	6	32,122,386	G	C	0.892	1.06 (1.03-1.08)	6.1×10^{-6}	1.06 (1.03-1.09)	6.3×10^{-6}	1.11 (1.02-1.20)	0.047
	BTNL2 p.Ser83Gly	rs2076530	6	32,363,816	C	T	0.416	1.02 (1.01-1.04)	0.00047	1.03 (1.01-1.06)	0.022	1.03 (1.01-1.05)	0.00091
	HLA-DQB1 p.Phe41Tyr	rs9274407	6	32,632,832	T	A	0.81	1.04 (1.02-1.06)	5.2×10^{-5}	1.05 (1.03-1.08)	2.7×10^{-5}	1.05 (0.99-1.11)	0.18

<i>PAX4</i>	<i>PAX4</i> p.Arg190His	rs2233580	7	127,253,550	T	C	0.084	1.39 (1.26-1.52)	1.4x10 ⁻¹²	2.04 (1.35-3.09)	0.00022	1.40 (1.27-1.54)	1.1x10 ⁻¹¹
<i>LPL</i>	<i>LPL</i> p.Ser474*	rs328	8	19,819,724	C	G	0.905	1.05 (1.02-1.07)	3.1x10 ⁻⁵	1.11 (1.01-1.22)	0.026	1.05 (1.02-1.08)	6.2x10 ⁻⁵
<i>SLC30A8</i>	<i>SLC30A8</i> p.Arg276Trp	rs13266634	8	118,184,783	C	T	0.69	1.08 (1.07-1.10)	7.4x10 ⁻²⁶	1.10 (1.08-1.12)	9.1x10 ⁻²³	1.13 (1.09-1.17)	2.0x10 ⁻¹²
<i>GP5M1</i>	<i>GP5M1</i> p.Ser391Leu	rs60980157	9	139,235,415	C	T	0.768	1.07 (1.05-1.09)	5.9x10 ⁻¹⁵	1.07 (1.05-1.10)	2.2x10 ⁻¹²	1.13 (1.08-1.18)	2.5x10 ⁻⁸
<i>KCNJ11-ABCC8</i>	<i>NUCB2</i> p.Gln338Glu	rs757081	11	17,351,683	G	C	0.316	1.05 (1.03-1.06)	3.3x10 ⁻⁷	1.07 (1.03-1.10)	0.00071	1.06 (1.03-1.08)	1.7x10 ⁻⁶
	<i>KCNJ11</i> p.Val250Ile	rs5215	11	17,408,630	C	T	0.368	1.06 (1.04-1.07)	1.6x10 ⁻¹³	1.09 (1.06-1.12)	3.2x10 ⁻⁹	1.07 (1.05-1.09)	2.9x10 ⁻¹⁰
	<i>KCNJ11</i> p.Lys29Glu	rs5219	11	17,409,572	T	C	0.367	1.06 (1.04-1.07)	4.2x10 ⁻¹⁴	1.09 (1.06-1.12)	3.8x10 ⁻¹⁰	1.07 (1.05-1.09)	1.7x10 ⁻¹⁰
	<i>ABCC8</i> p.Ala1369Ser	rs757110	11	17,418,477	C	A	0.37	1.05 (1.04-1.07)	4.4x10 ⁻¹²	1.09 (1.06-1.12)	2.3x10 ⁻¹⁰	1.06 (1.04-1.08)	6.1x10 ⁻⁸
<i>PLCB3</i>	<i>PLCB3</i> p.Ser778Leu	rs35169799	11	64,031,241	T	C	0.061	1.03 (1.00-1.06)	0.011	1.03 (1.00-1.07)	0.007	1.01 (0.87-1.17)	0.78
<i>TPCN2</i>	<i>TPCN2</i> p.Val219Ile	rs72928978	11	68,831,364	G	A	0.888	1.05 (1.03-1.08)	2.1x10 ⁻⁷	1.06 (1.03-1.09)	5.8x10 ⁻⁷	1.09 (1.01-1.18)	0.017
	<i>TPCN2</i> p.Met484Leu	rs35264875	11	68,846,399	A	T	0.852	1.08 (1.05-1.11)	3.4x10 ⁻⁸	1.15 (1.05-1.25)	9.6x10 ⁻⁵	1.08 (1.05-1.12)	3.1x10 ⁻⁷
<i>CENTD2</i>	<i>ARAP1</i> p.Gln802Glu	rs56200889	11	72,408,055	G	C	0.73	1.03 (1.02-1.05)	7.0x10 ⁻⁵	1.04 (1.02-1.06)	0.00024	1.05 (1.01-1.09)	0.0073
<i>KLHDC5</i>	<i>MRPS35</i> p.Gly43Arg	rs1127787	12	27,867,727	G	A	0.854	1.06 (1.04-1.08)	5.8x10 ⁻⁸	1.06 (1.04-1.09)	1.1x10 ⁻⁷	1.09 (1.02-1.16)	0.0057
	<i>MANSC4</i> p.Thr163Met	rs11049125	12	27,916,206	G	A	0.852	1.05 (1.03-1.07)	1.1x10 ⁻⁶	1.06 (1.04-1.08)	2.2x10 ⁻⁶	1.09 (1.02-1.16)	0.014
	<i>MANSC4</i> p.Leu157Ser	rs11049126	12	27,916,224	A	G	0.852	1.05 (1.03-1.07)	1.5x10 ⁻⁶	1.09 (1.02-1.16)	0.016	1.06 (1.03-1.08)	2.8x10 ⁻⁶
<i>WSCD2</i>	<i>WSCD2</i> p.Thr113Ile	rs3764002	12	108,618,630	C	T	0.714	1.03 (1.01-1.04)	5.4x10 ⁻⁵	1.03 (1.01-1.05)	0.00062	1.04 (1.01-1.08)	0.0007
<i>HNF1A</i>	<i>HNF1A</i> p.Ile75Leu	rs1169288	12	121,416,650	C	A	0.323	1.04 (1.02-1.05)	1.1x10 ⁻⁶	1.08 (1.04-1.12)	2.9x10 ⁻⁶	1.03 (1.01-1.06)	0.00063
	<i>HNF1A</i> p.Ala146Val	rs1800574	12	121,416,864	T	C	0.03	1.10 (1.05-1.15)	2.5x10 ⁻⁵	1.10 (1.05-1.16)	2.5x10 ⁻⁵	1.08 (0.77-1.50)	0.26
<i>MPHOSPH9</i>	<i>SBNO1</i> p.Ser729Asn	rs1060105	12	123,806,219	C	T	0.818	1.04 (1.02-1.06)	3.5x10 ⁻⁶	1.06 (1.03-1.08)	2.3x10 ⁻⁷	1.01 (0.96-1.06)	0.47
<i>ZZEF1</i>	<i>ZZEF1</i> p.Ile402Val	rs781831	17	3,947,644	C	T	0.425	1.04 (1.03-1.06)	3.3x10 ⁻⁹	1.07 (1.05-1.10)	3.6x10 ⁻⁸	1.04 (1.02-1.07)	1.8x10 ⁻⁵
	<i>ZZEF1</i> p.Leu360Pro	rs781852	17	3,953,102	G	A	0.402	1.04 (1.03-1.06)	1.1x10 ⁻⁸	1.08 (1.05-1.10)	1.2x10 ⁻⁷	1.04 (1.02-1.06)	2.9x10 ⁻⁵
<i>MLX</i>	<i>MLX</i> p.Gln139Arg	rs665268	17	40,722,029	G	A	0.301	1.03 (1.02-1.05)	3.4x10 ⁻⁶	1.04 (1.01-1.08)	0.0097	1.04 (1.02-1.06)	6.7x10 ⁻⁶
<i>TTLL6-CALCOCO2</i>	<i>TTLL6</i> p.Glu712Asp	rs2032844	17	46,847,364	C	A	0.76	1.03 (1.02-1.05)	0.00035	1.04 (1.02-1.06)	0.0014	1.05 (1.01-1.10)	0.0084
	<i>CALCOCO2</i> p.Pro347Ala	rs10278	17	46,939,658	C	G	0.712	1.04 (1.02-1.05)	2.7x10 ⁻⁶	1.05 (1.01-1.09)	0.0032	1.05 (1.03-1.07)	8.6x10 ⁻⁶
<i>C17orf58</i>	<i>C17orf58</i> p.Ile92Val	rs9891146	17	65,988,049	T	C	0.346	1.03 (1.02-1.05)	1.1x10 ⁻⁵	1.06 (1.02-1.09)	0.00029	1.03 (1.01-1.06)	0.00026
<i>CILP2</i>	<i>NCAN</i> p.Pro92Ser	rs2228603	19	19,329,924	T	C	0.071	1.08 (1.05-1.11)	7.1x10 ⁻⁸	1.08 (1.04-1.11)	1.2x10 ⁻⁶	1.33 (1.16-1.53)	2.6x10 ⁻⁵
	<i>TM6SF2</i> p.Glu167Lys	rs58542926	19	19,379,549	T	C	0.077	1.08 (1.06-1.11)	5.5x10 ⁻¹⁰	1.08 (1.05-1.11)	2.0x10 ⁻⁸	1.29 (1.15-1.46)	5.2x10 ⁻⁶
	<i>ZNF101</i> Splice region	rs2304130	19	19,789,528	G	A	0.102	1.04 (1.02-1.06)	0.00043	1.13 (1.04-1.24)	0.00077	1.04 (1.01-1.06)	0.0035
<i>GIPR</i>	<i>GIPR</i> p.Glu318Gln	rs1800437	19	46,181,392	C	G	0.2	1.03 (1.01-1.05)	0.0024	1.03 (1.01-1.05)	0.012	1.06 (1.02-1.12)	0.01
<i>ZHX3</i>	<i>ZHX3</i> p.Asn310Ser	rs17265513	20	39,832,628	C	T	0.172	1.04 (1.02-1.06)	1.1x10 ⁻⁵	1.08 (1.03-1.14)	0.00065	1.04 (1.02-1.07)	4.8x10 ⁻⁵
<i>HNF4A</i>	<i>HNF4A</i> p.Thr139Ile	rs1800961	20	43,042,364	T	C	0.032	1.08 (1.04-1.13)	1.4x10 ⁻⁵	1.09 (1.04-1.13)	7.2x10 ⁻⁶	1.06 (0.78-1.42)	0.98
<i>MTMR3-ASCC2</i>	<i>ASCC2</i> p.Pro423Ser	rs36571	22	30,200,713	G	A	0.933	1.08 (1.05-1.11)	7.2x10 ⁻⁷	1.08 (1.05-1.11)	1.3x10 ⁻⁶	1.16 (1.01-1.33)	0.011
	<i>ASCC2</i> p.Asp407His	rs28265	22	30,200,761	C	G	0.928	1.09 (1.06-1.12)	3.0x10 ⁻⁸	1.17 (1.03-1.33)	0.0054	1.09 (1.06-1.12)	6.0x10 ⁻⁸
	<i>ASCC2</i> p.Val123Ile	rs11549795	22	30,221,120	C	T	0.929	1.08 (1.05-1.11)	9.8x10 ⁻⁸	1.08 (1.05-1.12)	1.6x10 ⁻⁷	1.14 (1.01-1.30)	0.012
	<i>MTMR3</i> p.Asn960Ser	rs41278853	22	30,416,527	A	G	0.929	1.08 (1.05-1.11)	2.6x10 ⁻⁸	1.18 (1.04-1.34)	0.0036	1.09 (1.06-1.12)	6.8x10 ⁻⁸
<i>PNPLA3</i>	<i>PNPLA3</i> p.Ile148Met	rs738409	22	44,324,727	G	C	0.241	1.04 (1.03-1.06)	7.1x10 ⁻⁸	1.09 (1.05-1.14)	1.4x10 ⁻⁵	1.04 (1.02-1.06)	9.0x10 ⁻⁶
<i>PIM3</i>	<i>PIM3</i> p.Val300Ala	rs4077129	22	50,356,693	T	C	0.283	1.04 (1.02-1.06)	1.3x10 ⁻⁷	1.08 (1.04-1.12)	1.0x10 ⁻⁵	1.04 (1.02-1.06)	2.5x10 ⁻⁵

(ii) BMI adjusted analyses.

Locus	Variant annotation	rs ID	Chr	Position	Alleles		RAF	Additive		Recessive		Dominant	
					Risk	Other		OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
MACF1	MACF1 p.Ile39Val	rs16826069	1	39,797,055	G	A	0.210	1.05 (1.03-1.07)	1.3x10 ⁻⁹	1.11 (1.07-1.16)	3.4x10 ⁻⁸	1.05 (1.03-1.07)	4.7x10 ⁻⁷
	MACF1 p.Lys1625Asn	rs41270807	1	39,801,815	C	A	0.195	1.05 (1.03-1.07)	1.8x10 ⁻⁷	1.12 (1.07-1.18)	3.3x10 ⁻⁶	1.05 (1.03-1.07)	1.5x10 ⁻⁵
	MACF1 p.Met1424Val	rs2296172	1	39,835,817	G	A	0.187	1.05 (1.03-1.06)	2.7x10 ⁻⁸	1.12 (1.07-1.17)	2.6x10 ⁻⁷	1.04 (1.02-1.06)	5.8x10 ⁻⁶
	MACF1 p.Ala3354Thr	rs587404	1	39,908,506	A	G	0.301	1.03 (1.02-1.04)	7.3x10 ⁻⁶	1.04 (1.02-1.05)	7.1x10 ⁻⁵	1.05 (1.02-1.08)	0.00065
FAM63A	FAM63A p.Tyr95Asn	rs140386498	1	150,972,959	A	T	0.988	1.21 (1.14-1.29)	1.2x10 ⁻⁶	1.66 (0.83-3.32)	0.46	1.21 (1.14-1.29)	7.6x10 ⁻⁷
GCKR	GCKR p.Pro446Leu	rs1260326	2	27,730,940	C	T	0.642	1.05 (1.04-1.07)	1.0x10 ⁻¹⁵	1.07 (1.05-1.09)	3.0x10 ⁻¹²	1.08 (1.05-1.11)	7.3x10 ⁻¹⁰
	C2orf16 p.Ile774Val	rs1919128	2	27,801,759	A	G	0.740	1.04 (1.02-1.05)	1.7x10 ⁻⁸	1.05 (1.02-1.09)	0.00052	1.05 (1.03-1.07)	9.2x10 ⁻⁸
	GPN1 p.Arg12Lys	rs3749147	2	27,851,918	G	A	0.771	1.04 (1.02-1.05)	8.7x10 ⁻⁷	1.04 (1.02-1.06)	1.4x10 ⁻⁵	1.06 (1.02-1.10)	0.0003
THADA	THADA p.Cys845Tyr	rs35720761	2	43,519,977	C	T	0.900	1.07 (1.05-1.09)	4.7x10 ⁻¹¹	1.08 (1.05-1.10)	6.6x10 ⁻¹²	1.06 (0.97-1.15)	0.23
	THADA p.Thr897Ala	rs7578597	2	43,732,823	T	C	0.900	1.05 (1.02-1.07)	6.3x10 ⁻⁵	1.03 (0.94-1.13)	0.30	1.05 (1.02-1.08)	4.4x10 ⁻⁵
CEP68	CEP68 p.Gly74Ser	rs7572857	2	65,296,798	G	A	0.849	1.05 (1.03-1.07)	2.4x10 ⁻⁶	1.05 (1.03-1.07)	4.7x10 ⁻⁶	1.09 (1.02-1.15)	0.020
GRB14	COBLL1 p.Asn901Asp	rs7607980	2	165,551,201	T	C	0.878	1.09 (1.07-1.11)	1.1x10 ⁻¹⁶	1.13 (1.05-1.22)	0.00059	1.10 (1.08-1.13)	1.6x10 ⁻¹⁶
PPARG	PPARG p.Pro12Ala	rs1801282	3	12,393,125	C	G	0.888	1.09 (1.06-1.11)	1.3x10 ⁻¹⁴	1.19 (1.10-1.30)	3.5x10 ⁻⁶	1.09 (1.06-1.12)	2.4x10 ⁻¹³
KIF9-PTPN23	KIF9 p.Arg638Trp	rs2276853	3	47,282,303	A	G	0.587	1.03 (1.02-1.04)	5.2x10 ⁻⁶	1.05 (1.03-1.07)	1.6x10 ⁻⁶	1.03 (1.00-1.05)	0.016
	PTPN23 p.Ala818Thr	rs6780013	3	47,452,118	G	A	0.628	1.03 (1.01-1.04)	2.2x10 ⁻⁵	1.04 (1.02-1.06)	2.9x10 ⁻⁵	1.03 (1.00-1.06)	0.016
IGF2BP2	SEN2 p.Thr291Lys	rs6762208	3	185,331,165	A	C	0.374	1.04 (1.02-1.05)	2.3x10 ⁻⁷	1.04 (1.02-1.06)	3.0x10 ⁻⁶	1.05 (1.03-1.08)	0.00041
WFS1	WFS1 p.Val333Ile	rs1801212	4	6,302,519	A	G	0.753	1.06 (1.05-1.08)	1.2x10 ⁻¹⁷	1.07 (1.05-1.09)	3.8x10 ⁻¹⁵	1.11 (1.07-1.15)	1.2x10 ⁻⁸
	WFS1 p.Arg611His	rs734312	4	6,303,354	A	G	0.543	1.05 (1.03-1.06)	7.8x10 ⁻¹¹	1.06 (1.03-1.08)	9.3x10 ⁻⁷	1.07 (1.05-1.10)	5.2x10 ⁻⁸
ANKH	ANKH p.Arg187Gln	rs146886108	5	14,751,305	C	T	0.996	1.20 (1.07-1.34)	0.0016	1.19 (1.07-1.34)	0.0016	2.59 (0.41-16.13)	0.38
POC5	POC5 p.His36Arg	rs2307111	5	75,003,678	T	C	0.551	1.02 (1.01-1.04)	0.0064	1.02 (1.00-1.05)	0.034	1.03 (1.01-1.05)	0.012
PAM-PP1P5K2	PAM p.Asp336Gly	rs35658696	5	102,338,811	G	A	0.0440	1.12 (1.08-1.16)	1.7x10 ⁻⁹	1.41 (1.13-1.76)	0.00071	1.12 (1.08-1.16)	6.9x10 ⁻⁹
	PP1P5K2 p.Ser1207Gly	rs36046591	5	102,537,285	G	A	0.0450	1.12 (1.08-1.16)	1.3x10 ⁻¹⁰	1.50 (1.22-1.85)	7.3x10 ⁻⁵	1.12 (1.08-1.16)	1.1x10 ⁻⁹
RREB1	RREB1 p.Asp1171Asn	rs9379084	6	7,231,843	G	A	0.889	1.09 (1.06-1.12)	4.9x10 ⁻¹¹	1.11 (1.07-1.14)	7.0x10 ⁻¹²	1.08 (0.98-1.19)	0.17
	RREB1 p.Ser1499Tyr	rs35742417	6	7,247,344	C	A	0.837	1.04 (1.02-1.06)	1.6x10 ⁻⁶	1.05 (1.03-1.07)	8.8x10 ⁻⁷	1.04 (0.99-1.10)	0.082
MHC	TCF19 p.Met131Val	rs2073721	6	31,129,616	G	A	0.747	1.04 (1.02-1.05)	1.4x10 ⁻⁶	1.04 (1.02-1.06)	5.0x10 ⁻⁵	1.08 (1.04-1.12)	2.9x10 ⁻⁵
	PRRC2A p.Leu1895Val	rs3132453	6	31,604,044	G	T	0.943	1.05 (1.02-1.08)	0.00015	1.06 (1.03-1.09)	4.3x10 ⁻⁵	1.00 (0.87-1.16)	0.94
	SLC44A4 p.Met250Val	rs644827	6	31,838,441	C	T	0.558	1.03 (1.01-1.04)	4.6x10 ⁻⁵	1.03 (1.01-1.05)	0.00094	1.04 (1.02-1.07)	0.00044
	SLC44A4 p.Val183Ile	rs2242665	6	31,839,309	T	C	0.558	1.03 (1.01-1.04)	3.6x10 ⁻⁵	1.03 (1.01-1.05)	0.0011	1.04 (1.02-1.07)	0.00024
	EHMT2 p.Ser58Phe	rs115884658	6	31,864,538	A	G	0.0290	1.12 (1.08-1.17)	5.3x10 ⁻⁶	1.12 (1.07-1.17)	6.7x10 ⁻⁶	1.48 (1.12-1.96)	0.059
	PPT2 p.Cys5Trp	rs3134604	6	32,122,386	G	C	0.892	1.05 (1.03-1.07)	1.0x10 ⁻⁵	1.06 (1.03-1.08)	3.9x10 ⁻⁶	1.07 (0.98-1.15)	0.19
	BTNL2 p.Ser83Gly	rs2076530	6	32,363,816	C	T	0.416	1.03 (1.02-1.04)	6.1x10 ⁻⁶	1.05 (1.02-1.07)	0.00062	1.04 (1.02-1.06)	7.0x10 ⁻⁵
	HLA-DQB1 p.Phe41Tyr	rs9274407	6	32,632,832	T	A	0.810	1.04 (1.02-1.06)	5.7x10 ⁻⁵	1.05 (1.03-1.08)	7.7x10 ⁻⁶	1.03 (0.97-1.09)	0.51
PAX4	PAX4 p.Arg190His	rs2233580	7	127,253,550	T	C	0.0840	1.38 (1.26-1.51)	2.6x10 ⁻¹²	2.04 (1.35-3.07)	0.00025	1.38 (1.26-1.53)	2.3x10 ⁻¹¹
LPL	LPL p.Ser474*	rs328	8	19,819,724	C	G	0.905	1.05 (1.02-1.07)	3.6x10 ⁻⁵	1.11 (1.02-1.21)	0.014	1.05 (1.02-1.07)	8.8x10 ⁻⁵
SLC30A8	SLC30A8 p.Arg276Trp	rs13266634	8	118,184,783	C	T	0.690	1.09 (1.07-1.10)	3.20E-34	1.10 (1.08-1.12)	8.4x10 ⁻³⁰	1.14 (1.11-1.17)	9.2x10 ⁻¹⁷
GPSM1	GPSM1 p.Ser391Leu	rs60980157	9	139,235,415	C	T	0.768	1.06 (1.05-1.08)	1.7x10 ⁻¹⁵	1.07 (1.05-1.09)	3.0x10 ⁻¹³	1.11 (1.07-1.16)	4.3x10 ⁻⁸
KCNJ11-ABCC8	NUCB2 p.Gln338Glu	rs757081	11	17,351,683	G	C	0.316	1.05 (1.04-1.07)	3.1x10 ⁻¹⁰	1.08 (1.04-1.11)	1.5x10 ⁻⁵	1.06 (1.04-1.09)	6.4x10 ⁻⁹
	KCNJ11 p.Val250Ile	rs5215	11	17,408,630	C	T	0.368	1.06 (1.05-1.08)	3.3x10 ⁻¹⁸	1.10 (1.07-1.13)	3.7x10 ⁻¹³	1.07 (1.05-1.09)	4.8x10 ⁻¹³

	KCNJ11 p.Lys29Glu	rs5219	11	17,409,572	T	C	0.367	1.06 (1.05-1.08)	4.7x10 ⁻¹⁸	1.10 (1.07-1.13)	2.8x10 ⁻¹³	1.07 (1.05-1.09)	6.6x10 ⁻¹³
	ABCC8 p.Ala1369Ser	rs757110	11	17,418,477	C	A	0.370	1.06 (1.04-1.07)	1.3x10 ⁻¹⁵	1.10 (1.07-1.13)	2.3x10 ⁻¹³	1.06 (1.04-1.08)	4.7x10 ⁻¹⁰
PLCB3	PLCB3 p.Ser778Leu	rs35169799	11	64,031,241	T	C	0.0610	1.05 (1.02-1.07)	0.00047	1.05 (1.02-1.08)	0.00019	1.00 (0.87-1.15)	0.76
TPCN2	TPCN2 p.Val219Ile	rs72928978	11	68,831,364	G	A	0.888	1.05 (1.03-1.07)	2.4x10 ⁻⁷	1.06 (1.03-1.08)	4.6x10 ⁻⁷	1.07 (1.00-1.15)	0.024
	TPCN2 p.Met484Leu	rs35264875	11	68,846,399	A	T	0.852	1.07 (1.04-1.10)	1.5x10 ⁻⁷	1.11 (1.02-1.21)	0.0006	1.08 (1.04-1.11)	6.3x10 ⁻⁷
CENTD2	ARAP1 p.Gln802Glu	rs56200889	11	72,408,055	G	C	0.730	1.04 (1.03-1.06)	9.2x10 ⁻⁸	1.05 (1.03-1.07)	8.3x10 ⁻⁷	1.07 (1.03-1.11)	0.00032
KLHDC5	MRPS35 p.Gly43Arg	rs1127787	12	27,867,727	G	A	0.854	1.05 (1.03-1.07)	5.8x10 ⁻⁷	1.06 (1.04-1.08)	4.9x10 ⁻⁷	1.06 (1.00-1.13)	0.029
	MANSC4 p.Thr163Met	rs11049125	12	27,916,206	G	A	0.852	1.05 (1.03-1.07)	3.9x10 ⁻⁶	1.05 (1.03-1.08)	4.3x10 ⁻⁶	1.07 (1.01-1.14)	0.041
	MANSC4 p.Leu157Ser	rs11049126	12	27,916,224	A	G	0.852	1.05 (1.03-1.07)	4.8x10 ⁻⁶	1.07 (1.01-1.14)	0.047	1.05 (1.03-1.08)	5.1x10 ⁻⁶
WSCD2	WSCD2 p.Thr113Ile	rs3764002	12	108,618,630	C	T	0.714	1.03 (1.01-1.04)	3.7x10 ⁻⁵	1.03 (1.01-1.05)	0.00028	1.04 (1.00-1.07)	0.0013
HNF1A	HNF1A p.Ile75Leu	rs1169288	12	121,416,650	C	A	0.323	1.04 (1.02-1.05)	3.4x10 ⁻⁷	1.08 (1.04-1.12)	8.6x10 ⁻⁷	1.03 (1.01-1.06)	0.00028
	HNF1A p.Ala146Val	rs1800574	12	121,416,864	T	C	0.0300	1.09 (1.05-1.14)	2.4x10 ⁻⁵	1.10 (1.05-1.14)	2.4x10 ⁻⁵	1.11 (0.81-1.51)	0.25
MPHOSPH9	SBNO1 p.Ser729Asn	rs1060105	12	123,806,219	C	T	0.818	1.04 (1.02-1.06)	9.2x10 ⁻⁷	1.05 (1.03-1.07)	9.6x10 ⁻⁸	1.02 (0.97-1.07)	0.28
ZZEF1	ZZEF1 p.Ile402Val	rs781831	17	3,947,644	C	T	0.425	1.03 (1.02-1.05)	2.2x10 ⁻⁷	1.06 (1.04-1.09)	3.1x10 ⁻⁷	1.03 (1.02-1.05)	0.0004
	ZZEF1 p.Leu360Pro	rs781852	17	3,953,102	G	A	0.402	1.04 (1.02-1.05)	5.2x10 ⁻⁷	1.06 (1.04-1.09)	1.5x10 ⁻⁶	1.04 (1.02-1.06)	0.00037
MLX	MLX p.Gln139Arg	rs665268	17	40,722,029	G	A	0.301	1.03 (1.01-1.04)	3.1x10 ⁻⁵	1.04 (1.00-1.07)	0.029	1.04 (1.02-1.06)	4.8x10 ⁻⁵
TTLL6-CALCOCO2	TTLL6 p.Glu712Asp	rs2032844	17	46,847,364	C	A	0.760	1.03 (1.01-1.04)	0.0050	1.03 (1.01-1.05)	0.007	1.03 (0.99-1.07)	0.094
	CALCOCO2 p.Pro347Ala	rs10278	17	46,939,658	C	G	0.712	1.03 (1.02-1.05)	6.0x10 ⁻⁵	1.04 (1.00-1.07)	0.016	1.04 (1.02-1.06)	9.8x10 ⁻⁵
C17orf58	C17orf58 p.Ile92Val	rs9891146	17	65,988,049	T	C	0.346	1.02 (1.00-1.03)	0.013	1.03 (1.00-1.06)	0.039	1.02 (1.00-1.04)	0.036
CILP2	NCAN p.Pro92Ser	rs2228603	19	19,329,924	T	C	0.0710	1.08 (1.05-1.11)	1.5x10 ⁻⁸	1.07 (1.04-1.10)	8.5x10 ⁻⁷	1.38 (1.22-1.57)	1.7x10 ⁻⁷
	TM6SF2 p.Glu167Lys	rs58542926	19	19,379,549	T	C	0.0770	1.09 (1.06-1.11)	5.6x10 ⁻¹²	1.08 (1.06-1.11)	8.4x10 ⁻¹⁰	1.35 (1.21-1.51)	4.3x10 ⁻⁸
	ZNF101 Splice region	rs2304130	19	19,789,528	G	A	0.102	1.05 (1.03-1.07)	5.5x10 ⁻⁶	1.17 (1.07-1.27)	2.8x10 ⁻⁵	1.05 (1.02-1.07)	0.00013
GIPR	GIPR p.Glu318Gln	rs1800437	19	46,181,392	C	G	0.200	1.05 (1.03-1.07)	6.1x10 ⁻⁹	1.05 (1.03-1.07)	1.2x10 ⁻⁷	1.09 (1.05-1.14)	0.00011
ZHX3	ZHX3 p.Asn310Ser	rs17265513	20	39,832,628	C	T	0.172	1.03 (1.02-1.05)	0.00012	1.08 (1.03-1.13)	0.00027	1.03 (1.01-1.05)	0.00086
HNF4A	HNF4A p.Thr139Ile	rs1800961	20	43,042,364	T	C	0.032	1.08 (1.04-1.12)	6.8x10 ⁻⁶	1.08 (1.04-1.13)	5.0x10 ⁻⁶	1.15 (0.87-1.52)	0.62
MTMR3-ASCC2	ASCC2 p.Pro423Ser	rs36571	22	30,200,713	G	A	0.933	1.08 (1.05-1.11)	2.9x10 ⁻⁸	1.08 (1.05-1.11)	8.4x10 ⁻⁸	1.18 (1.04-1.34)	0.0027
	ASCC2 p.Asp407His	rs28265	22	30,200,761	C	G	0.928	1.09 (1.06-1.12)	1.0x10 ⁻⁹	1.20 (1.06-1.35)	0.00081	1.09 (1.06-1.12)	3.9x10 ⁻⁹
	ASCC2 p.Val123Ile	rs11549795	22	30,221,120	C	T	0.929	1.08 (1.06-1.11)	3.9x10 ⁻⁹	1.09 (1.06-1.12)	1.1x10 ⁻⁸	1.17 (1.04-1.32)	0.0023
	MTMR3 p.Asn960Ser	rs41278853	22	30,416,527	A	G	0.929	1.08 (1.06-1.11)	1.6x10 ⁻⁹	1.19 (1.06-1.35)	0.00078	1.09 (1.06-1.12)	7.1x10 ⁻⁹
PNPLA3	PNPLA3 p.Ile148Met	rs738409	22	44,324,727	G	C	0.241	1.05 (1.03-1.06)	2.3x10 ⁻⁹	1.10 (1.06-1.14)	7.5x10 ⁻⁷	1.05 (1.03-1.07)	1.0x10 ⁻⁶
PIM3	PIM3 p.Val300Ala	rs4077129	22	50,356,693	T	C	0.283	1.04 (1.02-1.05)	8.1x10 ⁻⁷	1.08 (1.04-1.13)	1.9x10 ⁻⁵	1.04 (1.02-1.06)	7.3x10 ⁻⁵

(b) European meta-analysis of 41,066 cases and 136,024 controls.

(i) BMI unadjusted analyses.

Locus	Variant annotation	rs ID	Chr	Position	Alleles		RAF	Additive		Recessive		Dominant	
					Risk	Other		OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
MACF1	MACF1 p.Ile39Val	rs16826069	1	39,797,055	G	A	0.223	1.06 (1.04-1.08)	2.6x10 ⁻¹⁰	1.13 (1.07-1.19)	3.2x10 ⁻⁷	1.06 (1.03-1.08)	7.9x10 ⁻⁸
	MACF1 p.Lys1625Asn	rs41270807	1	39,801,815	C	A	0.217	1.06 (1.04-1.08)	2.4x10 ⁻⁹	1.15 (1.09-1.21)	4.7x10 ⁻⁷	1.06 (1.04-1.09)	6.5x10 ⁻⁷
	MACF1 p.Met1424Val	rs2296172	1	39,835,817	G	A	0.218	1.06 (1.04-1.08)	2.9x10 ⁻¹⁰	1.14 (1.08-1.20)	6.4x10 ⁻⁸	1.06 (1.03-1.08)	1.8x10 ⁻⁷
	MACF1 p.Ala3354Thr	rs587404	1	39,908,506	A	G	0.295	1.03 (1.02-1.05)	7.8x10 ⁻⁶	1.05 (1.01-1.10)	0.0012	1.04 (1.02-1.06)	8.9x10 ⁻⁵
FAM63A	FAM63A p.Tyr95Asn	rs140386498	1	150,972,959	A	T	0.986	1.25 (1.16-1.34)	6.5x10 ⁻⁹	1.25 (1.16-1.34)	7.8x10 ⁻⁹	2.03 (0.92-4.48)	0.14
GCKR	GCKR p.Pro446Leu	rs1260326	2	27,730,940	C	T	0.618	1.06 (1.04-1.07)	1.3x10 ⁻¹²	1.07 (1.05-1.10)	1.9x10 ⁻¹⁰	1.07 (1.04-1.11)	5.3x10 ⁻⁷
	C2orf16 p.Ile774Val	rs1919128	2	27,801,759	A	G	0.743	1.03 (1.02-1.05)	6.2x10 ⁻⁶	1.04 (1.02-1.07)	2.4x10 ⁻⁵	1.05 (1.00-1.09)	0.0057
	GPN1 p.Arg12Lys	rs3749147	2	27,851,918	G	A	0.752	1.03 (1.01-1.06)	2.1x10 ⁻⁵	1.04 (1.02-1.07)	0.00013	1.05 (1.00-1.10)	0.0035
THADA	THADA p.Cys845Tyr	rs35720761	2	43,519,977	C	T	0.892	1.07 (1.04-1.10)	2.4x10 ⁻⁹	1.08 (1.05-1.11)	4.7x10 ⁻¹⁰	1.06 (0.96-1.17)	0.27
	THADA p.Thr897Ala	rs7578597	2	43,732,823	T	C	0.914	1.07 (1.04-1.11)	2.2x10 ⁻⁶	1.08 (1.04-1.12)	1.7x10 ⁻⁶	1.09 (0.94-1.26)	0.21
CEP68	CEP68 p.Gly74Ser	rs7572857	2	65,296,798	G	A	0.831	1.05 (1.02-1.07)	6.1x10 ⁻⁵	1.05 (1.02-1.08)	0.00012	1.09 (1.02-1.17)	0.032
GRB14	COBLL1 p.Asn901Asp	rs7607980	2	165,551,201	T	C	0.881	1.08 (1.06-1.11)	1.4x10 ⁻¹¹	1.09 (1.06-1.12)	3.9x10 ⁻¹¹	1.15 (1.05-1.26)	0.0026
PPARG	PPARG p.Pro12Ala	rs1801282	3	12,393,125	C	G	0.869	1.07 (1.04-1.10)	3.4x10 ⁻⁸	1.07 (1.04-1.10)	9.0x10 ⁻⁸	1.15 (1.04-1.26)	0.0044
KIF9-PTPN23	KIF9 p.Arg638Trp	rs2276853	3	47,282,303	A	G	0.598	1.02 (1.00-1.04)	0.0047	1.03 (1.01-1.06)	0.0022	1.01 (0.98-1.05)	0.19
	PTPN23 p.Ala818Thr	rs6780013	3	47,452,118	G	A	0.616	1.02 (1.01-1.04)	0.0016	1.03 (1.01-1.06)	0.0024	1.02 (0.99-1.06)	0.055
IGF2BP2	SEN2 p.Thr291Lys	rs6762208	3	185,331,165	A	C	0.337	1.03 (1.02-1.05)	5.4x10 ⁻⁵	1.05 (1.02-1.09)	0.007	1.04 (1.02-1.06)	0.00021
WFS1	WFS1 p.Val333Ile	rs1801212	4	6,302,519	A	G	0.708	1.07 (1.05-1.09)	2.5x10 ⁻¹⁷	1.08 (1.06-1.11)	1.7x10 ⁻¹⁴	1.12 (1.08-1.16)	1.3x10 ⁻⁸
	WFS1 p.Arg611His	rs734312	4	6,303,354	A	G	0.530	1.05 (1.03-1.07)	1.2x10 ⁻¹⁰	1.06 (1.03-1.08)	1.2x10 ⁻⁶	1.08 (1.05-1.11)	1.6x10 ⁻⁸
ANKH	ANKH p.Arg187Gln	rs146886108	5	14,751,305	C	T	0.996	1.21 (1.07-1.37)	0.00080	1.21 (1.07-1.37)	0.00085	3.22 (0.46-22.36)	0.25
POC5	POC5 p.His36Arg	rs2307111	5	75,003,678	T	C	0.595	1.04 (1.03-1.06)	2.0x10 ⁻⁷	1.06 (1.03-1.09)	5.6x10 ⁻⁶	1.06 (1.03-1.10)	7.8x10 ⁻⁵
PAM-PPIP5K2	PAM p.Asp336Gly	rs35658696	5	102,338,811	G	A	0.051	1.12 (1.07-1.16)	1.5x10 ⁻⁸	1.31 (1.03-1.67)	0.021	1.12 (1.07-1.16)	2.6x10 ⁻⁸
	PPIP5K2 p.Ser1207Gly	rs36046591	5	102,537,285	G	A	0.051	1.12 (1.08-1.16)	2.9x10 ⁻⁹	1.43 (1.14-1.80)	0.0018	1.12 (1.07-1.16)	1.2x10 ⁻⁸
RREB1	RREB1 p.Asp1171Asn	rs9379084	6	7,231,843	G	A	0.888	1.09 (1.05-1.12)	6.7x10 ⁻⁸	1.10 (1.06-1.14)	5.1x10 ⁻⁸	1.11 (0.99-1.25)	0.057
	RREB1 p.Ser1499Tyr	rs35742417	6	7,247,344	C	A	0.806	1.04 (1.02-1.06)	2.0x10 ⁻⁵	1.05 (1.03-1.07)	8.6x10 ⁻⁶	1.04 (0.98-1.11)	0.18
MHC	TCF19 p.Met131Val	rs2073721	6	31,129,616	G	A	0.742	1.04 (1.02-1.05)	1.0x10 ⁻⁵	1.04 (1.01-1.06)	0.00017	1.08 (1.03-1.13)	0.00045
	PRRC2A p.Leu1895Val	rs3132453	6	31,604,044	G	T	0.928	1.06 (1.03-1.10)	2.9x10 ⁻⁵	1.07 (1.04-1.11)	1.6x10 ⁻⁵	1.06 (0.91-1.24)	0.42
	SLC44A4 p.Met250Val	rs644827	6	31,838,441	C	T	0.537	1.03 (1.01-1.04)	0.00015	1.03 (1.01-1.06)	0.0046	1.04 (1.02-1.07)	0.00071
	SLC44A4 p.Val183Ile	rs2242665	6	31,839,309	T	C	0.536	1.03 (1.01-1.05)	0.00011	1.03 (1.01-1.06)	0.0054	1.05 (1.02-1.08)	0.00034
	EHMT2 p.Ser58Phe	rs115884658	6	31,864,538	A	G	0.0320	1.10 (1.05-1.15)	0.00018	1.33 (0.98-1.81)	0.28	1.10 (1.05-1.15)	0.00018
	PPT2 p.Cys5Trp	rs3134604	6	32,122,386	G	C	0.870	1.06 (1.04-1.09)	6.9x10 ⁻⁷	1.07 (1.04-1.10)	6.1x10 ⁻⁷	1.10 (1.01-1.21)	0.064
	BTNL2 p.Ser83Gly	rs2076530	6	32,363,816	C	T	0.430	1.03 (1.01-1.05)	9.5x10 ⁻⁵	1.04 (1.01-1.07)	0.0024	1.04 (1.02-1.06)	0.00087
	HLA-DQB1 p.Phe41Tyr	rs9274407	6	32,632,832	T	A	0.816	1.05 (1.02-1.07)	8.8x10 ⁻⁵	1.06 (1.03-1.08)	4.3x10 ⁻⁵	1.05 (0.98-1.12)	0.26
PAX4	PAX4 p.Arg190His	rs2233580	7	127,253,550	T	C	N/A	N/A	N/A	N/A	N/A	N/A	N/A
LPL	LPL p.Ser474*	rs328	8	19,819,724	C	G	0.903	1.05 (1.02-1.08)	0.00024	1.05 (1.02-1.08)	0.00022	1.08 (0.97-1.20)	0.19
SLC30A8	SLC30A8 p.Arg276Trp	rs13266634	8	118,184,783	C	T	0.678	1.08 (1.06-1.10)	1.7x10 ⁻²⁰	1.09 (1.07-1.12)	4.3x10 ⁻¹⁸	1.12 (1.08-1.16)	8.4x10 ⁻¹⁰
GP5M1	GP5M1 p.Ser391Leu	rs60980157	9	139,235,415	C	T	0.744	1.07 (1.05-1.09)	5.4x10 ⁻¹⁵	1.08 (1.05-1.10)	2.3x10 ⁻¹²	1.13 (1.08-1.19)	3.8x10 ⁻⁸

KCNJ11-ABCC8	NUCB2 p.Gln338Glu	rs757081	11	17,351,683	G	C	0.341	1.05 (1.03-1.07)	6.2x10 ⁻⁸	1.08 (1.04-1.12)	8.7x10 ⁻⁵	1.06 (1.04-1.09)	1.5x10 ⁻⁶
	KCNJ11 p.Val250Ile	rs5215	11	17,408,630	C	T	0.394	1.06 (1.04-1.08)	1.4x10 ⁻¹³	1.09 (1.06-1.12)	6.9x10 ⁻⁹	1.07 (1.05-1.10)	3.4x10 ⁻¹⁰
	KCNJ11 p.Lys29Glu	rs5219	11	17,409,572	T	C	0.394	1.06 (1.04-1.08)	2.1x10 ⁻¹³	1.09 (1.06-1.12)	6.4x10 ⁻⁹	1.07 (1.05-1.10)	5.8x10 ⁻¹⁰
	ABCC8 p.Ala1369Ser	rs757110	11	17,418,477	C	A	0.394	1.06 (1.04-1.07)	5.6x10 ⁻¹²	1.09 (1.06-1.12)	2.2x10 ⁻⁹	1.06 (1.04-1.09)	6.1x10 ⁻⁸
PLCB3	PLCB3 p.Ser778Leu	rs35169799	11	64,031,241	T	C	0.0730	1.04 (1.01-1.07)	0.0022	1.01 (0.86-1.18)	0.66	1.04 (1.01-1.07)	0.0012
TPCN2	TPCN2 p.Val219Ile	rs72928978	11	68,831,364	G	A	0.850	1.05 (1.03-1.08)	1.6x10 ⁻⁵	1.05 (1.03-1.08)	4.0x10 ⁻⁵	1.09 (1.01-1.18)	0.026
	TPCN2 p.Met484Leu	rs35264875	11	68,846,399	A	T	0.821	1.07 (1.04-1.10)	1.5x10 ⁻⁶	1.08 (1.04-1.11)	1.0x10 ⁻⁵	1.14 (1.04-1.25)	0.0012
CENTD2	ARAP1 p.Gln802Glu	rs56200889	11	72,408,055	G	C	0.719	1.03 (1.01-1.06)	0.00050	1.04 (1.02-1.07)	0.00086	1.05 (1.00-1.10)	0.028
KLHDC5	MRPS35 p.Gly43Arg	rs1127787	12	27,867,727	G	A	0.842	1.06 (1.04-1.08)	4.7x10 ⁻⁸	1.07 (1.04-1.09)	7.7x10 ⁻⁸	1.09 (1.02-1.17)	0.012
	MANSC4 p.Thr163Met	rs11049125	12	27,916,206	G	A	0.843	1.06 (1.04-1.08)	8.6x10 ⁻⁸	1.07 (1.04-1.09)	2.3x10 ⁻⁷	1.10 (1.02-1.18)	0.0072
	MANSC4 p.Leu157Ser	rs11049126	12	27,916,224	A	G	0.843	1.06 (1.04-1.08)	1.1x10 ⁻⁷	1.07 (1.04-1.09)	2.7x10 ⁻⁷	1.10 (1.02-1.18)	0.0084
WSCD2	WSCD2 p.Thr113Ile	rs3764002	12	108,618,630	C	T	0.723	1.03 (1.01-1.05)	3.0x10 ⁻⁵	1.03 (1.01-1.05)	0.0019	1.07 (1.03-1.12)	3.7x10 ⁻⁵
HNF1A	HNF1A p.Ile75Leu	rs1169288	12	121,416,650	C	A	0.343	1.03 (1.01-1.05)	2.6x10 ⁻⁵	1.08 (1.04-1.13)	2.7x10 ⁻⁶	1.02 (1.00-1.05)	0.011
	HNF1A p.Ala146Val	rs1800574	12	121,416,864	T	C	0.0330	1.11 (1.06-1.16)	1.0x10 ⁻⁵	1.13 (0.80-1.60)	0.25	1.11 (1.06-1.16)	1.2x10 ⁻⁵
MPHOSPH9	SBNO1 p.Ser729Asn	rs1060105	12	123,806,219	C	T	0.796	1.04 (1.02-1.06)	3.8x10 ⁻⁵	1.05 (1.03-1.08)	1.9x10 ⁻⁶	1.00 (0.95-1.06)	0.78
ZZEF1	ZZEF1 p.Ile402Val	rs781831	17	3,947,644	C	T	0.404	1.05 (1.03-1.07)	3.3x10 ⁻⁹	1.08 (1.05-1.11)	4.4x10 ⁻⁷	1.05 (1.03-1.08)	2.9x10 ⁻⁶
	ZZEF1 p.Leu360Pro	rs781852	17	3,953,102	G	A	0.387	1.05 (1.04-1.07)	1.6x10 ⁻¹⁰	1.09 (1.06-1.12)	9.0x10 ⁻⁸	1.06 (1.04-1.08)	2.3x10 ⁻⁷
MLX	MLX p.Gln139Arg	rs665268	17	40,722,029	G	A	0.270	1.03 (1.01-1.05)	0.00012	1.04 (0.99-1.08)	0.047	1.04 (1.02-1.06)	0.00015
TTLL6-CALCOCO2	TTLL6 p.Glu712Asp	rs2032844	17	46,847,364	C	A	0.756	1.04 (1.02-1.06)	9.7x10 ⁻⁵	1.05 (1.02-1.07)	0.00038	1.06 (1.01-1.11)	0.0087
	CALCOCO2 p.Pro347Ala	rs10278	17	46,939,658	C	G	0.707	1.05 (1.03-1.06)	1.5x10 ⁻⁷	1.06 (1.04-1.08)	1.6x10 ⁻⁷	1.05 (1.01-1.09)	0.0060
C17orf58	C17orf58 p.Ile92Val	rs9891146	17	65,988,049	T	C	0.280	1.04 (1.02-1.06)	9.8x10 ⁻⁶	1.08 (1.04-1.13)	0.00021	1.04 (1.01-1.06)	0.00044
CILP2	NCAN p.Pro92Ser	rs2228603	19	19,329,924	T	C	0.0780	1.07 (1.03-1.10)	3.8x10 ⁻⁵	1.31 (1.13-1.52)	0.00013	1.06 (1.03-1.10)	0.00036
	TM6SF2 p.Glu167Lys	rs58542926	19	19,379,549	T	C	0.0800	1.09 (1.06-1.12)	6.8x10 ⁻⁹	1.33 (1.16-1.53)	1.2x10 ⁻⁵	1.08 (1.05-1.12)	2.2x10 ⁻⁷
	ZNF101 Splice region	rs2304130	19	19,789,528	G	A	0.0830	1.06 (1.03-1.10)	1.4x10 ⁻⁵	1.18 (1.04-1.35)	0.0039	1.06 (1.03-1.10)	6.6x10 ⁻⁵
GIPR	GIPR p.Glu318Gln	rs1800437	19	46,181,392	C	G	0.222	1.03 (1.01-1.05)	0.0061	1.06 (1.00-1.12)	0.034	1.03 (1.01-1.05)	0.019
ZHX3	ZHX3 p.Asn310Ser	rs17265513	20	39,832,628	C	T	0.214	1.04 (1.02-1.06)	4.6x10 ⁻⁶	1.07 (1.02-1.13)	0.013	1.05 (1.02-1.07)	8.2x10 ⁻⁶
HNF4A	HNF4A p.Thr139Ile	rs1800961	20	43,042,364	T	C	0.0360	1.07 (1.02-1.11)	0.00046	1.06 (0.77-1.46)	0.88	1.07 (1.02-1.12)	0.00031
MTMR3-ASCC2	ASCC2 p.Pro423Ser	rs36571	22	30,200,713	G	A	0.918	1.08 (1.05-1.11)	1.7x10 ⁻⁶	1.08 (1.05-1.12)	2.2x10 ⁻⁶	1.15 (1.00-1.33)	0.048
	ASCC2 p.Asp407His	rs28265	22	30,200,761	C	G	0.918	1.08 (1.05-1.12)	4.0x10 ⁻⁷	1.09 (1.05-1.12)	5.6x10 ⁻⁷	1.16 (1.01-1.33)	0.032
	ASCC2 p.Val123Ile	rs11549795	22	30,221,120	C	T	0.918	1.08 (1.05-1.11)	1.3x10 ⁻⁶	1.08 (1.05-1.12)	1.5x10 ⁻⁶	1.14 (0.99-1.31)	0.057
	MTMR3 p.Asn960Ser	rs41278853	22	30,416,527	A	G	0.918	1.08 (1.05-1.11)	2.4x10 ⁻⁷	1.09 (1.05-1.12)	3.8x10 ⁻⁷	1.17 (1.02-1.34)	0.026
PNPLA3	PNPLA3 p.Ile148Met	rs738409	22	44,324,727	G	C	0.229	1.04 (1.02-1.06)	5.6x10 ⁻⁶	1.11 (1.05-1.16)	1.8x10 ⁻⁵	1.04 (1.02-1.06)	0.00041
PIM3	PIM3 p.Val300Ala	rs4077129	22	50,356,693	T	C	0.260	1.03 (1.01-1.06)	9.6x10 ⁻⁵	1.07 (1.02-1.12)	0.0016	1.03 (1.01-1.06)	0.0018

(ii) BMI adjusted analyses.

Locus	Variant annotation	rs ID	Chr	Position	Alleles		RAF	Additive		Recessive		Dominant	
					Risk	Other		OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
MACF1	MACF1 p.Ile39Val	rs16826069	1	39,797,055	G	A	0.223	1.05 (1.03-1.07)	5.1x10 ⁻⁹	1.11 (1.06-1.17)	9.0x10 ⁻⁷	1.05 (1.03-1.07)	1.0x10 ⁻⁶
	MACF1 p.Lys1625Asn	rs41270807	1	39,801,815	C	A	0.217	1.05 (1.03-1.07)	8.7x10 ⁻⁸	1.13 (1.07-1.19)	1.5x10 ⁻⁶	1.05 (1.03-1.08)	1.3x10 ⁻⁵
	MACF1 p.Met1424Val	rs2296172	1	39,835,817	G	A	0.218	1.05 (1.03-1.07)	6.4x10 ⁻⁹	1.13 (1.07-1.18)	1.6x10 ⁻⁷	1.05 (1.03-1.07)	2.5x10 ⁻⁶

	MACF1 p.Ala3354Thr	rs587404	1	39,908,506	A	G	0.295	1.04 (1.02-1.05)	1.4x10 ⁻⁶	1.06 (1.02-1.10)	0.00012	1.04 (1.02-1.06)	5.1x10 ⁻⁵
FAM63A	FAM63A p.Tyr95Asn	rs140386498	1	150,972,959	A	T	0.986	1.23 (1.15-1.31)	7.7x10 ⁻⁹	1.22 (1.15-1.31)	1.1x10 ⁻⁸	2.23 (1.06-4.67)	0.054
GCKR	GCKR p.Pro446Leu	rs1260326	2	27,730,940	C	T	0.618	1.05 (1.04-1.07)	1.6x10 ⁻¹²	1.07 (1.04-1.09)	1.0x10 ⁻⁹	1.07 (1.04-1.10)	1.4x10 ⁻⁷
	C2orf16 p.Ile774Val	rs1919128	2	27,801,759	A	G	0.743	1.03 (1.02-1.05)	5.0x10 ⁻⁶	1.04 (1.02-1.06)	2.5x10 ⁻⁵	1.05 (1.00-1.09)	0.0038
	GPN1 p.Arg12Lys	rs3749147	2	27,851,918	G	A	0.752	1.03 (1.01-1.05)	2.3x10 ⁻⁵	1.04 (1.02-1.06)	0.00012	1.05 (1.00-1.09)	0.0041
THADA	THADA p.Cys845Tyr	rs35720761	2	43,519,977	C	T	0.892	1.07 (1.05-1.10)	6.0x10 ⁻¹¹	1.08 (1.06-1.11)	5.8x10 ⁻¹²	1.05 (0.95-1.15)	0.32
	THADA p.Thr897Ala	rs7578597	2	43,732,823	T	C	0.914	1.07 (1.04-1.10)	7.3x10 ⁻⁷	1.08 (1.04-1.11)	2.8x10 ⁻⁷	1.05 (0.91-1.21)	0.40
CEP68	CEP68 p.Gly74Ser	rs7572857	2	65,296,798	G	A	0.831	1.04 (1.02-1.06)	3.8x10 ⁻⁵	1.04 (1.02-1.07)	9.5x10 ⁻⁵	1.09 (1.02-1.16)	0.020
GRB14	COBLL1 p.Asn901Asp	rs7607980	2	165,551,201	T	C	0.881	1.09 (1.07-1.12)	5.7x10 ⁻¹⁵	1.10 (1.07-1.13)	1.4x10 ⁻¹⁴	1.14 (1.05-1.25)	0.00076
PPARG	PPARG p.Pro12Ala	rs1801282	3	12,393,125	C	G	0.869	1.08 (1.06-1.11)	3.5x10 ⁻¹²	1.09 (1.06-1.12)	1.8x10 ⁻¹¹	1.17 (1.08-1.28)	0.00029
KIF9-PTPN23	KIF9 p.Arg638Trp	rs2276853	3	47,282,303	A	G	0.598	1.03 (1.01-1.04)	6.2x10 ⁻⁵	1.04 (1.02-1.06)	0.00011	1.03 (1.00-1.06)	0.018
	PTPN23 p.Ala818Thr	rs6780013	3	47,452,118	G	A	0.616	1.03 (1.01-1.05)	1.9x10 ⁻⁵	1.04 (1.02-1.06)	8.0x10 ⁻⁵	1.03 (1.00-1.06)	0.0053
IGF2BP2	SEN2 p.Thr291Lys	rs6762208	3	185,331,165	A	C	0.337	1.03 (1.02-1.05)	1.1x10 ⁻⁵	1.06 (1.02-1.09)	0.0037	1.04 (1.02-1.06)	4.3x10 ⁻⁵
WFS1	WFS1 p.Val333Ile	rs1801212	4	6,302,519	A	G	0.708	1.06 (1.05-1.08)	7.6x10 ⁻¹⁵	1.07 (1.05-1.10)	1.9x10 ⁻¹²	1.10 (1.06-1.14)	2.2x10 ⁻⁷
	WFS1 p.Arg611His	rs734312	4	6,303,354	A	G	0.530	1.05 (1.03-1.06)	1.0x10 ⁻⁹	1.05 (1.03-1.08)	1.6x10 ⁻⁶	1.07 (1.04-1.10)	3.1x10 ⁻⁷
ANKH	ANKH p.Arg187Gln	rs146886108	5	14,751,305	C	T	0.996	1.21 (1.08-1.36)	0.00062	1.21 (1.07-1.35)	0.00062	2.59 (0.40-16.85)	0.39
POC5	POC5 p.His36Arg	rs2307111	5	75,003,678	T	C	0.595	1.03 (1.01-1.04)	0.0012	1.03 (1.01-1.05)	0.011	1.04 (1.01-1.07)	0.0045
PAM-PP1P5K2	PAM p.Asp336Gly	rs35658696	5	102,338,811	G	A	0.0510	1.12 (1.08-1.16)	2.2x10 ⁻⁹	1.37 (1.09-1.72)	0.0056	1.12 (1.07-1.16)	6.1x10 ⁻⁹
	PP1P5K2 p.Ser1207Gly	rs36046591	5	102,537,285	G	A	0.0510	1.12 (1.08-1.16)	4.2x10 ⁻¹⁰	1.47 (1.18-1.82)	0.00054	1.12 (1.08-1.16)	2.6x10 ⁻⁹
RREB1	RREB1 p.Asp1171Asn	rs9379084	6	7,231,843	G	A	0.888	1.09 (1.05-1.12)	5.3x10 ⁻⁹	1.10 (1.06-1.13)	1.2x10 ⁻⁹	1.07 (0.95-1.19)	0.16
	RREB1 p.Ser1499Tyr	rs35742417	6	7,247,344	C	A	0.806	1.04 (1.02-1.06)	2.0x10 ⁻⁵	1.04 (1.02-1.07)	1.4x10 ⁻⁵	1.05 (0.99-1.11)	0.11
MHC	TCF19 p.Met131Val	rs2073721	6	31,129,616	G	A	0.742	1.04 (1.02-1.06)	7.9x10 ⁻⁷	1.04 (1.02-1.06)	4.8x10 ⁻⁵	1.08 (1.04-1.13)	3.0x10 ⁻⁵
	PRRC2A p.Leu1895Val	rs3132453	6	31,604,044	G	T	0.928	1.05 (1.02-1.08)	0.00038	1.06 (1.03-1.09)	0.00016	1.01 (0.87-1.16)	0.83
	SLC44A4 p.Met250Val	rs644827	6	31,838,441	C	T	0.537	1.03 (1.02-1.05)	2.5x10 ⁻⁵	1.04 (1.01-1.06)	0.0011	1.05 (1.02-1.07)	0.00022
	SLC44A4 p.Val183Ile	rs2242665	6	31,839,309	T	C	0.536	1.03 (1.02-1.05)	1.7x10 ⁻⁵	1.04 (1.01-1.06)	0.0013	1.05 (1.02-1.08)	9.3x10 ⁻⁵
	EHMT2 p.Ser58Phe	rs115884658	6	31,864,538	A	G	0.0320	1.13 (1.08-1.17)	5.9x10 ⁻⁷	1.48 (1.11-1.97)	0.065	1.12 (1.08-1.17)	7.7x10 ⁻⁷
	PPT2 p.Cys5Trp	rs3134604	6	32,122,386	G	C	0.870	1.06 (1.03-1.08)	2.4x10 ⁻⁶	1.06 (1.04-1.09)	8.4x10 ⁻⁷	1.06 (0.97-1.15)	0.29
	BTNL2 p.Ser83Gly	rs2076530	6	32,363,816	C	T	0.430	1.04 (1.02-1.05)	3.2x10 ⁻⁷	1.06 (1.03-1.09)	1.9x10 ⁻⁵	1.05 (1.02-1.07)	3.6x10 ⁻⁵
	HLA-DQB1 p.Phe41Tyr	rs9274407	6	32,632,832	T	A	0.816	1.04 (1.02-1.06)	8.1x10 ⁻⁵	1.06 (1.03-1.08)	1.3x10 ⁻⁵	1.03 (0.97-1.09)	0.64
PAX4	PAX4 p.Arg190His	rs2233580	7	127,253,550	T	C	N/A	N/A	N/A	N/A	N/A	N/A	N/A
LPL	LPL p.Ser474*	rs328	8	19,819,724	C	G	0.903	1.05 (1.02-1.07)	0.00014	1.05 (1.02-1.08)	0.00016	1.08 (0.98-1.20)	0.12
SLC30A8	SLC30A8 p.Arg276Trp	rs13266634	8	118,184,783	C	T	0.678	1.08 (1.06-1.10)	6.3x10 ²⁵	1.09 (1.07-1.12)	1.8x10 ²¹	1.13 (1.09-1.17)	2.2x10 ⁻¹²
GP5M1	GP5M1 p.Ser391Leu	rs60980157	9	139,235,415	C	T	0.744	1.07 (1.05-1.09)	2.1x10 ⁻¹⁵	1.08 (1.05-1.10)	3.0x10 ⁻¹³	1.12 (1.07-1.17)	1.6x10 ⁻⁷
KCNJ11-ABCC8	NUCB2 p.Gln338Glu	rs757081	11	17,351,683	G	C	0.341	1.06 (1.04-1.08)	2.0x10 ⁻¹¹	1.09 (1.05-1.14)	6.6x10 ⁻⁷	1.07 (1.05-1.10)	4.6x10 ⁻⁹
	KCNJ11 p.Val250Ile	rs5215	11	17,408,630	C	T	0.394	1.07 (1.05-1.08)	8.5x10 ⁻¹⁸	1.10 (1.07-1.13)	1.8x10 ⁻¹²	1.08 (1.06-1.10)	2.3x10 ⁻¹²
	KCNJ11 p.Lys29Glu	rs5219	11	17,409,572	T	C	0.394	1.07 (1.05-1.08)	1.5x10 ⁻¹⁷	1.10 (1.07-1.13)	1.6x10 ⁻¹²	1.08 (1.05-1.10)	4.4x10 ⁻¹²
	ABCC8 p.Ala1369Ser	rs757110	11	17,418,477	C	A	0.394	1.06 (1.05-1.08)	8.9x10 ⁻¹⁶	1.10 (1.07-1.13)	7.5x10 ⁻¹³	1.07 (1.05-1.09)	6.9x10 ⁻¹⁰
PLCB3	PLCB3 p.Ser778Leu	rs35169799	11	64,031,241	T	C	0.0730	1.05 (1.02-1.08)	3.9x10 ⁻⁵	1.00 (0.87-1.16)	0.68	1.06 (1.03-1.09)	1.2x10 ⁻⁵
TPCN2	TPCN2 p.Val219Ile	rs72928978	11	68,831,364	G	A	0.850	1.05 (1.02-1.07)	1.2x10 ⁻⁵	1.05 (1.03-1.08)	1.9x10 ⁻⁵	1.07 (0.99-1.15)	0.056
	TPCN2 p.Met484Leu	rs35264875	11	68,846,399	A	T	0.821	1.07 (1.04-1.10)	2.9x10 ⁻⁶	1.07 (1.04-1.11)	8.7x10 ⁻⁶	1.11 (1.02-1.21)	0.007
CENTD2	ARAP1 p.Gln802Glu	rs56200889	11	72,408,055	G	C	0.719	1.05 (1.03-1.07)	4.3x10 ⁻⁷	1.06 (1.03-1.08)	2.1x10 ⁻⁶	1.07 (1.03-1.12)	0.0011
KLHDC5	MRPS35 p.Gly43Arg	rs1127787	12	27,867,727	G	A	0.842	1.05 (1.03-1.07)	8.6x10 ⁻⁷	1.06 (1.04-1.08)	6.3x10 ⁻⁷	1.06 (1.00-1.14)	0.060

	MANSC4 p.Thr163Met	rs11049125	12	27,916,206	G	A	0.843	1.05 (1.03-1.07)	6.3x10 ⁻⁷	1.06 (1.03-1.08)	8.3x10 ⁻⁷	1.08 (1.01-1.15)	0.031
	MANSC4 p.Leu157Ser	rs11049126	12	27,916,224	A	G	0.843	1.05 (1.03-1.07)	7.5x10 ⁻⁷	1.06 (1.03-1.08)	9.5x10 ⁻⁷	1.07 (1.01-1.15)	0.034
WSCD2	WSCD2 p.Thr113Ile	rs3764002	12	108,618,630	C	T	0.723	1.03 (1.01-1.05)	3.6x10 ⁻⁵	1.03 (1.01-1.05)	0.00096	1.06 (1.01-1.10)	0.00024
HNF1A	HNF1A p.Ile75Leu	rs1169288	12	121,416,650	C	A	0.343	1.03 (1.01-1.05)	1.7x10 ⁻⁵	1.08 (1.04-1.12)	1.7x10 ⁻⁶	1.02 (1.00-1.05)	0.0078
	HNF1A p.Ala146Val	rs1800574	12	121,416,864	T	C	0.0330	1.10 (1.05-1.14)	9.0x10 ⁻⁶	1.16 (0.84-1.60)	0.23	1.10 (1.05-1.15)	1.1x10 ⁻⁵
MPHOSPH9	SBNO1 p.Ser729Asn	rs1060105	12	123,806,219	C	T	0.796	1.04 (1.02-1.06)	1.3x10 ⁻⁵	1.05 (1.03-1.07)	1.3x10 ⁻⁶	1.01 (0.96-1.07)	0.44
ZZEF1	ZZEF1 p.Ile402Val	rs781831	17	3,947,644	C	T	0.404	1.04 (1.02-1.05)	2.2x10 ⁻⁷	1.06 (1.04-1.10)	4.1x10 ⁻⁶	1.04 (1.02-1.06)	8.3x10 ⁻⁵
	ZZEF1 p.Leu360Pro	rs781852	17	3,953,102	G	A	0.387	1.04 (1.03-1.06)	1.7x10 ⁻⁸	1.07 (1.04-1.10)	2.6x10 ⁻⁶	1.05 (1.03-1.07)	5.6x10 ⁻⁶
MLX	MLX p.Gln139Arg	rs665268	17	40,722,029	G	A	0.270	1.03 (1.01-1.04)	0.00088	1.03 (0.99-1.07)	0.13	1.03 (1.01-1.05)	0.00072
TTLL6-CALCOCO2	TTLL6 p.Glu712Asp	rs2032844	17	46,847,364	C	A	0.756	1.03 (1.01-1.05)	0.0014	1.04 (1.02-1.06)	0.002	1.04 (0.99-1.08)	0.073
	CALCOCO2 p.Pro347Ala	rs10278	17	46,939,658	C	G	0.707	1.04 (1.02-1.06)	3.6x10 ⁻⁶	1.05 (1.03-1.07)	2.0x10 ⁻⁶	1.04 (1.00-1.08)	0.028
C17orf58	C17orf58 p.Ile92Val	rs9891146	17	65,988,049	T	C	0.280	1.02 (1.00-1.04)	0.0091	1.04 (1.00-1.09)	0.025	1.02 (0.99-1.04)	0.042
CILP2	NCAN p.Pro92Ser	rs2228603	19	19,329,924	T	C	0.0780	1.08 (1.05-1.11)	4.5x10 ⁻⁷	1.34 (1.17-1.54)	1.5x10 ⁻⁵	1.07 (1.04-1.10)	8.9x10 ⁻⁶
	TM6SF2 p.Glu167Lys	rs58542926	19	19,379,549	T	C	0.0800	1.09 (1.06-1.12)	5.7x10 ⁻¹¹	1.38 (1.21-1.57)	3.5x10 ⁻⁷	1.09 (1.06-1.12)	6.0x10 ⁻⁹
	ZNF101 Splice region	rs2304130	19	19,789,528	G	A	0.0830	1.08 (1.05-1.11)	2.4x10 ⁻⁸	1.25 (1.11-1.41)	9.1x10 ⁻⁵	1.07 (1.04-1.11)	4.5x10 ⁻⁷
GIPR	GIPR p.Glu318Gln	rs1800437	19	46,181,392	C	G	0.222	1.05 (1.04-1.07)	7.8x10 ⁻⁹	1.09 (1.04-1.15)	0.00059	1.06 (1.04-1.08)	6.8x10 ⁻⁸
ZHX3	ZHX3 p.Asn310Ser	rs17265513	20	39,832,628	C	T	0.214	1.03 (1.01-1.05)	8.1x10 ⁻⁵	1.07 (1.02-1.13)	0.0084	1.03 (1.01-1.06)	0.00032
HNF4A	HNF4A p.Thr139Ile	rs1800961	20	43,042,364	T	C	0.0360	1.07 (1.02-1.11)	0.00026	1.15 (0.86-1.56)	0.72	1.07 (1.02-1.11)	0.00023
MTMR3-ASCC2	ASCC2 p.Pro423Ser	rs36571	22	30,200,713	G	A	0.918	1.08 (1.05-1.11)	4.2x10 ⁻⁸	1.09 (1.05-1.12)	9.1x10 ⁻⁸	1.17 (1.03-1.34)	0.012
	ASCC2 p.Asp407His	rs28265	22	30,200,761	C	G	0.918	1.09 (1.06-1.12)	8.9x10 ⁻⁹	1.09 (1.06-1.12)	2.3x10 ⁻⁸	1.19 (1.04-1.35)	0.0064
	ASCC2 p.Val123Ile	rs11549795	22	30,221,120	C	T	0.918	1.08 (1.05-1.11)	2.7x10 ⁻⁸	1.09 (1.06-1.12)	5.6x10 ⁻⁸	1.17 (1.03-1.33)	0.013
	MTMR3 p.Asn960Ser	rs41278853	22	30,416,527	A	G	0.918	1.08 (1.06-1.11)	1.0x10 ⁻⁸	1.09 (1.06-1.12)	3.0x10 ⁻⁸	1.19 (1.05-1.36)	0.0058
PNPLA3	PNPLA3 p.Ile148Met	rs738409	22	44,324,727	G	C	0.229	1.04 (1.03-1.06)	4.8x10 ⁻⁷	1.11 (1.06-1.16)	1.2x10 ⁻⁶	1.04 (1.02-1.06)	0.00011
PIM3	PIM3 p.Val300Ala	rs4077129	22	50,356,693	T	C	0.260	1.03 (1.01-1.05)	0.00014	1.07 (1.02-1.11)	0.0011	1.03 (1.01-1.05)	0.0027

Chr: chromosome. RAF: risk allele frequency. OR: odds ratio. CI: confidence interval.

Supplementary Table 5 | Index coding variants for distinct T2D association signals attaining exome-wide significance ($p < 2.2 \times 10^{-7}$) in trans-ethnic meta-analysis of 73,033 cases and 362,354 controls in the discovery analysis.

(a) Summary of conditional analysis of index coding variants.

Locus	Variant annotation	rs ID	Chr	Position	Alleles		RAF	Conditioning variant	BMI unadjusted		BMI adjusted	
					Risk	Other			OR (95% CI)	p-value	OR (95% CI)	p-value
<i>MACF1</i>	<i>MACF1</i> p.Met1424Val	rs2296172	1	39,835,817	G	A	0.193	Unconditional	1.06 (1.05-1.08)	6.7×10^{-16}	1.04 (1.03-1.06)	5.9×10^{-8}
<i>FAM63A</i>	<i>FAM63A</i> p.Tyr95Asn	rs140386498	1	150,972,959	A	T	0.988	Unconditional	1.21 (1.14-1.28)	7.5×10^{-8}	1.19 (1.12-1.26)	6.7×10^{-7}
<i>GCKR</i>	<i>GCKR</i> p.Pro446Leu	rs1260326	2	27,730,940	C	T	0.630	Unconditional	1.06 (1.05-1.08)	5.3×10^{-25}	1.06 (1.04-1.07)	3.2×10^{-18}
<i>THADA</i>	<i>THADA</i> p.Cys845Tyr	rs35720761	2	43,519,977	C	T	0.895	Unconditional	1.08 (1.05-1.10)	4.6×10^{-15}	1.07 (1.05-1.10)	8.3×10^{-16}
<i>CEP68</i>	<i>CEP68</i> p.Gly74Ser	rs7572857	2	65,296,798	G	A	0.846	Unconditional	1.05 (1.04-1.07)	8.3×10^{-9}	1.05 (1.03-1.07)	6.6×10^{-7}
<i>GRB14</i>	<i>COBLL1</i> p.Asn901Asp	rs7607980	2	165,551,201	T	C	0.879	Unconditional	1.08 (1.06-1.11)	8.6×10^{-20}	1.09 (1.07-1.12)	5.0×10^{-23}
<i>PPARG</i>	<i>PPARG</i> p.Pro12Ala	rs1801282	3	12,393,125	C	G	0.887	Unconditional	1.09 (1.07-1.11)	1.4×10^{-17}	1.10 (1.07-1.12)	2.7×10^{-19}
<i>KIF9</i>	<i>KIF9</i> p.Arg638Trp	rs2276853	3	47,282,303	A	G	0.588	Unconditional	1.02 (1.01-1.04)	8.0×10^{-5}	1.03 (1.02-1.05)	5.3×10^{-8}
<i>IGF2BP2</i>	<i>SEN2</i> p.Thr291Lys	rs6762208	3	185,331,165	A	C	0.367	Unconditional	1.03 (1.01-1.04)	1.6×10^{-6}	1.03 (1.02-1.05)	3.0×10^{-8}
<i>WFS1</i>	<i>WFS1</i> p.Val333Ile	rs1801212	4	6,302,519	A	G	0.748	Unconditional	1.07 (1.06-1.09)	1.1×10^{-24}	1.07 (1.05-1.08)	7.1×10^{-21}
<i>ANKH</i>	<i>ANKH</i> p.Arg187Gln	rs146886108	5	14,751,305	C	T	0.996	Unconditional	1.29 (1.16-1.45)	1.4×10^{-7}	1.27 (1.13-1.41)	3.5×10^{-7}
<i>POC5</i>	<i>POC5</i> p.His36Arg	rs2307111	5	75,003,678	T	C	0.562	Unconditional	1.05 (1.04-1.07)	1.6×10^{-15}	1.03 (1.01-1.04)	2.1×10^{-5}
<i>PAM-PIIP5K2</i>	<i>PAM</i> p.Asp336Gly	rs35658696	5	102,338,811	G	A	0.0450	Unconditional	1.13 (1.10-1.17)	1.2×10^{-16}	1.13 (1.09-1.17)	7.4×10^{-15}
<i>RREB1</i>	<i>RREB1</i> p.Asp1171Asn	rs9379084	6	7,231,843	G	A	0.884	<i>RREB1</i> p.Ser1499Tyr	1.08 (1.06-1.11)	3.1×10^{-13}	1.10 (1.07-1.13)	8.5×10^{-17}
	<i>RREB1</i> p.Ser1499Tyr	rs35742417	6	7,247,344	C	A	0.836	<i>RREB1</i> p.Asp1171Asn	1.04 (1.03-1.06)	2.3×10^{-9}	1.05 (1.02-1.07)	7.5×10^{-10}
<i>MHC</i>	<i>TCF19</i> p.Met131Val	rs2073721	6	31,129,616	G	A	0.749	Unconditional	1.04 (1.02-1.05)	1.6×10^{-10}	1.04 (1.02-1.05)	2.3×10^{-9}
<i>PAX4</i>	<i>PAX4</i> p.Arg190His	rs2233580	7	127,253,550	T	C	0.0294	Unconditional	1.36 (1.25-1.48)	1.8×10^{-12}	1.38 (1.26-1.51)	4.2×10^{-13}
<i>LPL</i>	<i>LPL</i> p.Ser474*	rs328	8	19,819,724	C	G	0.903	Unconditional	1.05 (1.03-1.08)	6.8×10^{-9}	1.05 (1.03-1.07)	2.3×10^{-7}
<i>SLC30A8</i>	<i>SLC30A8</i> p.Arg276Trp	rs13266634	8	118,184,783	C	T	0.691	Unconditional	1.09 (1.08-1.11)	1.9×10^{-47}	1.09 (1.08-1.11)	1.3×10^{-47}
<i>GPSM1</i>	<i>GPSM1</i> p.Ser391Leu	rs60980157	9	139,235,415	C	T	0.771	Unconditional	1.06 (1.05-1.08)	3.2×10^{-16}	1.06 (1.05-1.08)	6.6×10^{-16}
<i>KCNJ11-ABCC8</i>	<i>KCNJ11</i> p.Lys29Glu	rs5219	11	17,409,572	T	C	0.364	Unconditional	1.06 (1.05-1.07)	5.7×10^{-22}	1.07 (1.05-1.08)	1.5×10^{-22}
<i>PLCB3</i>	<i>PLCB3</i> p.Ser778Leu	rs35169799	11	64,031,241	T	C	0.0585	Unconditional	1.04 (1.02-1.07)	0.00012	1.05 (1.03-1.08)	1.7×10^{-6}
<i>TPCN2</i>	<i>TPCN2</i> p.Val219Ile	rs72928978	11	68,831,364	G	A	0.890	Unconditional	1.05 (1.02-1.07)	5.2×10^{-7}	1.05 (1.03-1.07)	1.8×10^{-8}
<i>CENTD2</i>	<i>ARAP1</i> p.Gln802Glu	rs56200889	11	72,408,055	G	C	0.733	Unconditional	1.04 (1.02-1.05)	4.8×10^{-8}	1.05 (1.03-1.06)	5.2×10^{-10}
<i>KLHDC5</i>	<i>MRPS35</i> p.Gly43Arg	rs1127787	12	27,867,727	G	A	0.850	Unconditional	1.06 (1.04-1.08)	1.4×10^{-11}	1.05 (1.03-1.07)	1.5×10^{-8}
<i>WSCD2</i>	<i>WSCD2</i> p.Thr113Ile	rs3764002	12	108,618,630	C	T	0.719	Unconditional	1.03 (1.02-1.05)	3.3×10^{-8}	1.03 (1.02-1.05)	1.2×10^{-7}
<i>HNF1A</i>	<i>HNF1A</i> p.Ile75Leu	rs1169288	12	121,416,650	C	A	0.323	<i>HNF1A</i> p.Ala146Val	1.05 (1.03-1.08)	1.3×10^{-8}	1.05 (1.02-1.06)	1.5×10^{-7}
	<i>HNF1A</i> p.Ala146Val	rs1800574	12	121,416,864	T	C	0.029	<i>HNF1A</i> p.Ile75Leu	1.10 (1.05-1.14)	1.3×10^{-6}	1.10 (1.06-1.15)	6.9×10^{-7}
<i>MPHOSPH9</i>	<i>SBNO1</i> p.Ser729Asn	rs1060105	12	123,806,219	C	T	0.815	Unconditional	1.04 (1.02-1.06)	5.7×10^{-7}	1.04 (1.02-1.06)	1.1×10^{-7}
<i>ZZEF1</i>	<i>ZZEF1</i> p.Ile402Val	rs781831	17	3,947,644	C	T	0.422	Unconditional	1.04 (1.03-1.05)	8.3×10^{-11}	1.03 (1.02-1.05)	1.8×10^{-7}
<i>MLX</i>	<i>MLX</i> p.Gln139Arg	rs665268	17	40,722,029	G	A	0.294	Unconditional	1.04 (1.02-1.05)	2.0×10^{-8}	1.03 (1.02-1.04)	1.1×10^{-5}
<i>TTLL6</i>	<i>TTLL6</i> p.Glu712Asp	rs2032844	17	46,847,364	C	A	0.754	Unconditional	1.04 (1.02-1.06)	1.2×10^{-7}	1.03 (1.01-1.04)	0.00098
<i>C17orf58</i>	<i>C17orf58</i> p.Ile92Val	rs9891146	17	65,988,049	T	C	0.332	Unconditional	1.04 (1.02-1.05)	7.2×10^{-7}	1.02 (1.00-1.03)	0.0027
<i>CILP2</i>	<i>TM6SF2</i> p.Glu167Lys	rs58542926	19	19,379,549	T	C	0.0755	Unconditional	1.07 (1.05-1.10)	4.8×10^{-12}	1.09 (1.06-1.11)	3.4×10^{-15}

<i>GIPR</i>	<i>GIPR</i> p.Glu318Gln	rs1800437	19	46,181,392	C	G	0.200	Unconditional	1.03 (1.02-1.05)	7.1x10 ⁻⁵	1.06 (1.04-1.07)	6.8x10 ⁻¹²
<i>ZHX3</i>	<i>ZHX3</i> p.Asn310Ser	rs17265513	20	39,832,628	C	T	0.174	Unconditional	1.04 (1.02-1.06)	6.8x10 ⁻⁶	1.04 (1.02-1.05)	3.2x10 ⁻⁵
<i>HNF4A</i>	<i>HNF4A</i> p.Thr139Ile	rs1800961	20	43,042,364	T	C	0.0316	Unconditional	1.09 (1.05-1.13)	2.6x10 ⁻⁸	1.10 (1.06-1.14)	5.0x10 ⁻⁸
<i>MTMR3-ASCC2</i>	<i>ASCC2</i> p.Asp407His	rs28265	22	30,200,761	C	G	0.925	Unconditional	1.09 (1.06-1.11)	2.1x10 ⁻¹²	1.09 (1.07-1.12)	4.4x10 ⁻¹⁴
<i>PNPLA3</i>	<i>PNPLA3</i> p.Ile148Met	rs738409	22	44,324,727	G	C	0.239	Unconditional	1.04 (1.03-1.05)	2.1x10 ⁻¹⁰	1.05 (1.03-1.06)	2.8x10 ⁻¹¹
<i>PIM3</i>	<i>PIM3</i> p.Val300Ala	rs4077129	22	50,356,693	T	C	0.276	Unconditional	1.04 (1.02-1.05)	1.9x10 ⁻⁷	1.04 (1.02-1.06)	3.5x10 ⁻⁸

(b) Summary of conditional analysis of index coding variants and non-coding GWAS lead variants.

Locus	Index coding variant	rs ID	Chr	Position	Alleles		RAF	BMI unadjusted		BMI adjusted		Conditioning variant	BMI unadjusted	BMI adjusted
					Risk	Other		OR (95% CI)	p-value	OR (95% CI)	p-value		p-value	p-value
<i>GCKR</i>	<i>GCKR</i> p.Pro446Leu	rs1260326	2	27,730,940	C	T	0.630	1.06 (1.05-1.08)	5.3x10 ⁻²⁵	1.06 (1.04-1.07)	3.2x10 ⁻¹⁸	rs780094	1.0x10 ⁻⁵	1.5x10 ⁻⁶
		rs780094	2	27,741,237	C	T	0.634	1.06 (1.05-1.07)	6.8x10 ⁻²²	1.06 (1.04-1.07)	1.8x10 ⁻¹⁷	<i>GCKR</i> p.Pro446Leu	0.094	0.22
<i>THADA</i>	<i>THADA</i> p.Cys845Tyr	rs35720761	2	43,519,977	C	T	0.895	1.08 (1.05-1.10)	4.6x10 ⁻¹⁵	1.07 (1.05-1.10)	8.3x10 ⁻¹⁶	rs10495903	4.9x10 ⁻⁶	6.8x10 ⁻⁷
		rs10495903	2	43,806,918	C	T	0.878	1.06 (1.04-1.08)	2.6x10 ⁻¹⁰	1.05 (1.03-1.07)	7.9x10 ⁻⁸	<i>THADA</i> p.Cys845Tyr	0.25	0.61
<i>GRB14</i>	<i>COBLL1</i> p.Asn901Asp	rs7607980	2	165,551,201	T	C	0.879	1.08 (1.06-1.11)	8.6x10 ⁻²⁰	1.09 (1.07-1.12)	5.0x10 ⁻²³	rs13389219	1.2x10 ⁻⁵	1.2x10 ⁻⁶
		rs13389219	2	165,528,876	C	T	0.622	1.07 (1.05-1.08)	2.8x10 ⁻²⁴	1.07 (1.06-1.09)	1.3x10 ⁻²⁹	<i>COBLL1</i> p.Asn901Asp	3.1x10 ⁻¹³	4.0x10 ⁻¹⁷
<i>IGF2BP2</i>	<i>SEN2</i> p.Thr291Lys	rs6762208	3	185,331,165	A	C	0.367	1.03 (1.01-1.04)	1.6x10 ⁻⁶	1.03 (1.02-1.05)	3.0x10 ⁻⁸	rs4402960	0.54	0.87
		rs4402960	3	185,511,687	T	G	0.333	1.10 (1.09-1.11)	7.4x10 ⁻⁵⁴	1.10 (1.08-1.11)	8.3x10 ⁻⁴⁹	<i>SEN2</i> p.Thr291Lys	4.2x10 ⁻⁴⁷	3.1x10 ⁻³⁹
<i>WFS1</i>	<i>WFS1</i> p.Val333Ile	rs1801212	4	6,302,519	A	G	0.748	1.07 (1.06-1.09)	1.1x10 ⁻²⁴	1.07 (1.05-1.08)	7.1x10 ⁻²¹	rs1801214	3.9x10 ⁻⁵	2.3x10 ⁻⁶
		rs1801214	4	6,303,022	T	C	0.637	1.06 (1.05-1.07)	9.9x10 ⁻²¹	1.05 (1.04-1.07)	3.2x10 ⁻¹⁵	<i>WFS1</i> p.Val333Ile	0.0019	0.014
<i>RREB1</i>	<i>RREB1</i> p.Asp1171Asn	rs9379084	6	7,231,843	G	A	0.884	1.08 (1.06-1.11)	3.1x10 ⁻¹³	1.10 (1.07-1.13)	8.5x10 ⁻¹⁷	rs9505118	1.4x10 ⁻⁷	3.4x10 ⁻¹⁰
		rs9505118	6	7,290,437	A	G	0.599	1.04 (1.02-1.05)	2.0x10 ⁻⁸	1.04 (1.02-1.05)	7.6x10 ⁻⁹	<i>RREB1</i> p.Asp1171Asn	1.0x10 ⁻⁶	2.2x10 ⁻⁶
	<i>RREB1</i> p.Ser1499Tyr	rs35742417	6	7,247,344	C	A	0.836	1.04 (1.03-1.06)	2.3x10 ⁻⁹	1.05 (1.02-1.07)	7.5x10 ⁻¹⁰	rs9505118	0.0014	0.0051
		rs9505118	6	7,290,437	A	G	0.599	1.04 (1.02-1.05)	2.0x10 ⁻⁸	1.04 (1.02-1.05)	7.6x10 ⁻⁹	<i>RREB1</i> p.Ser1499Tyr	0.00011	3.3x10 ⁻⁵
<i>SLC30A8</i>	<i>SLC30A8</i> p.Arg276Trp	rs13266634	8	118,184,783	C	T	0.691	1.09 (1.08-1.11)	1.9x10 ⁻⁴⁷	1.09 (1.08-1.11)	1.3x10 ⁻⁴⁷	rs3802177	2.3x10 ⁻⁵	6.1x10 ⁻⁴
		rs3802177	8	118,185,025	G	A	0.690	1.09 (1.08-1.11)	3.1x10 ⁻⁴¹	1.09 (1.08-1.11)	2.4x10 ⁻⁴⁰	<i>SLC30A8</i> p.Arg276Trp	0.61	0.98
<i>CENTD2</i>	<i>ARAP1</i> p.Gln802Glu	rs56200889	11	72,408,055	G	C	0.733	1.04 (1.02-1.05)	4.8x10 ⁻⁸	1.05 (1.03-1.06)	5.2x10 ⁻¹⁰	rs11603334	0.94	0.80
		rs11603334	11	72,432,985	G	A	0.851	1.07 (1.06-1.09)	9.5x10 ⁻¹⁸	1.09 (1.07-1.11)	1.7x10 ⁻²⁴	<i>ARAP1</i> p.Gln802Glu	7.8x10 ⁻¹⁰	6.2x10 ⁻¹⁶
<i>KLHDC5</i>	<i>MRPS35</i> p.Gly43Arg	rs1127787	12	27,867,727	G	A	0.850	1.06 (1.04-1.08)	1.4x10 ⁻¹¹	1.05 (1.03-1.07)	1.5x10 ⁻⁸	rs10842994	0.0029	0.039
		rs10842994	12	27,965,150	C	T	0.824	1.06 (1.05-1.08)	9.4x10 ⁻¹⁶	1.06 (1.04-1.08)	7.6x10 ⁻¹³	<i>MRPS35</i> p.Gly43Arg	7.0x10 ⁻⁸	4.1x10 ⁻⁸
<i>HNF1A</i>	<i>HNF1A</i> p.Ile75Leu	rs1169288	12	121,416,650	C	A	0.323	1.05 (1.03-1.08)	1.3x10 ⁻⁸	1.05 (1.02-1.06)	1.5x10 ⁻⁷	rs7957197	8.6x10 ⁻⁶	1.2x10 ⁻⁵
		rs7957197	12	121,460,686	T	A	0.818	1.04 (1.02-1.06)	2.5x10 ⁻⁹	1.05 (1.02-1.06)	3.3x10 ⁻⁷	<i>HNF1A</i> p.Ile75Leu	1.7x10 ⁻⁵	9.9x10 ⁻⁵
	<i>HNF1A</i> p.Ala146Val	rs1800574	12	121,416,864	T	C	0.029	1.10 (1.05-1.14)	1.3x10 ⁻⁶	1.10 (1.06-1.15)	6.9x10 ⁻⁷	rs7957197	4.1x10 ⁻⁶	7.9x10 ⁻⁶
		rs7957197	12	121,460,686	T	A	0.818	1.04 (1.02-1.06)	2.5x10 ⁻⁹	1.05 (1.02-1.06)	3.3x10 ⁻⁷	<i>HNF1A</i> p.Ala146Val	2.2x10 ⁻⁸	2.1x10 ⁻⁶
<i>MPHOSPH9</i>	<i>SBNO1</i> p.Ser729Asn	rs1060105	12	123,806,219	C	T	0.815	1.04 (1.02-1.06)	5.7x10 ⁻⁷	1.04 (1.02-1.06)	1.1x10 ⁻⁷	rs1727307	0.46	0.27
		rs1727307	12	123,575,742	G	A	0.694	1.04 (1.03-1.05)	3.2x10 ⁻¹⁰	1.04 (1.03-1.05)	6.2x10 ⁻¹⁰	<i>SBNO1</i> p.Ser729Asn	0.00013	0.00012
<i>CILP2</i>	<i>TM6SF2</i> p.Glu167Lys	rs58542926	19	19,379,549	T	C	0.0755	1.07 (1.05-1.10)	4.8x10 ⁻¹²	1.09 (1.06-1.11)	3.4x10 ⁻¹⁵	rs10401969	0.16	0.19
		rs10401969	19	19,407,718	C	T	0.086	1.07 (1.04-1.09)	5.6x10 ⁻⁹	1.08 (1.06-1.10)	9.2x10 ⁻¹²	<i>TM6SF2</i> p.Glu167Lys	0.90	0.48
<i>GIPR</i>	<i>GIPR</i> p.Glu318Gln	rs1800437	19	46,181,392	C	G	0.200	1.03 (1.02-1.05)	7.1x10 ⁻⁵	1.06 (1.04-1.07)	6.8x10 ⁻¹²	rs8108269	0.0071	9.7x10 ⁻⁹
		rs8108269	19	46,158,513	G	T	0.328	1.06 (1.04-1.07)	8.3x10 ⁻¹⁷	1.06 (1.04-1.07)	5.2x10 ⁻¹⁶	<i>GIPR</i> p.Glu318Gln	8.3x10 ⁻¹²	1.0x10 ⁻¹¹
<i>HNF4A</i>	<i>HNF4A</i> p.Thr139Ile	rs1800961	20	43,042,364	T	C	0.0316	1.09 (1.05-1.13)	2.6x10 ⁻⁸	1.10 (1.06-1.14)	5.0x10 ⁻⁸	rs4812831	4.8x10 ⁻⁸	8.6x10 ⁻⁹
		rs4812831	20	43,018,260	A	G	0.130	1.06 (1.04-1.08)	8.5x10 ⁻¹⁰	1.06 (1.04-1.08)	1.3x10 ⁻⁸	<i>HNF4A</i> p.Thr139Ile	8.5x10 ⁻⁹	4.9x10 ⁻⁹

Chr: chromosome. RAF: risk allele frequency. BMI: body mass index. OR: odds ratio. CI: confidence interval.

Supplementary Table 6 | Comparison of summary statistics for T2D coding variant association signals obtained from trans-ethnic meta-analysis of: (i) 73,033 cases and 362,354 controls in the present study; and (ii) 34,809 cases and 57,985 controls from the T2D-GENES/GoT2D study.

Locus	Variant	rs ID	Chr	Position	Alleles		RAF	Trans-ethnic meta-analysis				Trans-ethnic meta-analysis from T2D-GENES/GoT2D	
					Risk	Other		BMI unadjusted		BMI adjusted			
								OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
GCKR	GCKR p.Pro446Leu	rs1260326	2	27,730,940	C	T	0.630	1.06 (1.05-1.08)	5.3x10 ⁻²⁵	1.06 (1.04-1.07)	3.2x10 ⁻¹⁸	1.07 (1.04-1.10)	1.2x10 ⁻⁹
THADA	THADA p.Cys845Tyr	rs35720761	2	43,519,977	C	T	0.895	1.08 (1.05-1.10)	4.6x10 ⁻¹⁵	1.07 (1.05-1.10)	8.3x10 ⁻¹⁶	1.12 (1.07-1.16)	3.3x10 ⁻¹⁰
GRB14	COBLL1 p.Asn901Asp	rs7607980	2	165,551,201	T	C	0.879	1.08 (1.06-1.11)	8.6x10 ⁻²⁰	1.09 (1.07-1.12)	5.0x10 ⁻²³	1.15 (1.11-1.19)	8.3x10 ⁻¹⁵
PPARG	PPARG p.Pro12Ala	rs1801282	3	12,393,125	C	G	0.887	1.09 (1.07-1.11)	1.4x10 ⁻¹⁷	1.10 (1.07-1.12)	2.7x10 ⁻¹⁹	1.11 (1.07-1.15)	4.2x10 ⁻⁸
WFS1	WFS1 p.Val333Ile	rs1801212	4	6,302,519	A	G	0.748	1.07 (1.06-1.09)	1.1x10 ⁻²⁴	1.07 (1.05-1.08)	7.1x10 ⁻²¹	1.09 (1.06-1.12)	9.0x10 ⁻¹⁴
PAM-PPIP5K2	PAM p.Asp336Gly	rs35658696	5	102,338,811	G	A	0.0450	1.13 (1.10-1.17)	1.2x10 ⁻¹⁶	1.13 (1.09-1.17)	7.4x10 ⁻¹⁵	1.17 (1.11-1.24)	5.7x10 ⁻¹⁰
RREB1	RREB1 p.Asp1171Asn	rs9379084	6	7,231,843	G	A	0.884	1.08 (1.06-1.11)	3.1x10 ⁻¹³	1.10 (1.07-1.13)	8.5x10 ⁻¹⁷	1.13 (1.09-1.18)	4.0x10 ⁻⁹
PAX4	PAX4 p.Arg190His	rs2233580	7	127,253,550	T	C	0.0294	1.36 (1.25-1.48)	1.8x10 ⁻¹²	1.38 (1.26-1.51)	4.2x10 ⁻¹³	1.79 (1.47-2.19)	9.3x10 ⁻⁹
SLC30A8	SLC30A8 p.Arg276Trp	rs13266634	8	118,184,783	C	T	0.691	1.09 (1.08-1.11)	1.9x10 ⁻⁴⁷	1.09 (1.08-1.11)	1.3x10 ⁻⁴⁷	1.14 (1.11-1.17)	4.8x10 ⁻²³
GPSM1	GPSM1 p.Ser391Leu	rs60980157	9	139,235,415	C	T	0.771	1.06 (1.05-1.08)	3.2x10 ⁻¹⁶	1.06 (1.05-1.08)	6.6x10 ⁻¹⁶	1.09 (1.06-1.12)	1.7x10 ⁻⁹
KCNJ11-ABCC8	KCNJ11 p.Lys29Glu	rs5219	11	17,409,572	T	C	0.364	1.06 (1.05-1.07)	5.7x10 ⁻²²	1.07 (1.05-1.08)	1.5x10 ⁻²²	1.07 (1.05-1.10)	9.0x10 ⁻¹⁰
CILP2	TM6SF2 p.Glu167Lys	rs58542926	19	19,379,549	T	C	0.0755	1.07 (1.05-1.10)	4.8x10 ⁻¹²	1.09 (1.06-1.11)	3.4x10 ⁻¹⁵	1.14 (1.10-1.19)	3.2x10 ⁻¹⁰
MTMR3-ASCC2	ASCC2 p.Asp407His	rs28265	22	30,200,761	C	G	0.925	1.09 (1.06-1.11)	2.1x10 ⁻¹²	1.09 (1.07-1.12)	4.4x10 ⁻¹⁴	1.12 (1.08-1.17)	1.1x10 ⁻⁷

Chr: chromosome. RAF: risk allele frequency. BMI: body mass index. OR: odds ratio. CI: confidence interval.

Supplementary Table 7 | Lead SNPs for non-coding T2D association signals attaining genome-wide significance ($p < 5 \times 10^{-8}$) that map outside previously established susceptibility loci.

(a) Trans-ethnic meta- analyses of 73,033 cases and 362,354 controls.

Locus	Lead SNP	Chr	Position	Alleles		RAF	BMI unadjusted		BMI adjusted	
				Risk	Other		OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value
<i>Loci overlapping with novel coding association signals</i>										
<i>POC5-ANKDD1B</i>	rs40060	5	74,967,386	T	C	0.597	1.04 (1.03-1.06)	1.3x10 ⁻¹²	1.02 (1.01-1.04)	0.00038
<i>LPL</i>	rs17482753	8	19,832,646	G	T	0.904	1.06 (1.04-1.08)	4.1x10 ⁻⁸	1.05 (1.03-1.07)	5.6x10 ⁻⁷
<i>C17orf58-BPTF</i>	rs12602912	17	65,870,073	T	C	0.238	1.04 (1.03-1.06)	4.7x10 ⁻⁹	1.03 (1.01-1.04)	0.00016
<i>Loci not overlapping with novel coding association signals</i>										
<i>MRAS</i>	rs2306374	3	138,119,952	C	T	0.136	1.04 (1.02-1.06)	6.5x10 ⁻⁶	1.05 (1.03-1.07)	1.9x10 ⁻⁷
<i>FAM13A</i>	rs13133548	4	89,740,128	A	G	0.490	1.03 (1.02-1.04)	8.3x10 ⁻⁷	1.03 (1.02-1.05)	5.0x10 ⁻⁸
<i>VEGFA</i>	rs6905288	6	43,758,873	A	G	0.603	1.03 (1.02-1.05)	5.5x10 ⁻⁷	1.04 (1.03-1.05)	5.8x10 ⁻¹¹
<i>TFAP2B</i>	rs2206277	6	50,798,526	T	C	0.195	1.05 (1.03-1.07)	4.3x10 ⁻¹⁰	1.02 (1.00-1.03)	0.022
<i>ABO</i>	rs505922	9	136,149,229	C	T	0.371	1.04 (1.03-1.05)	9.1x10 ⁻¹⁰	1.03 (1.02-1.04)	9.4x10 ⁻⁷
<i>PLEKHA1</i>	rs6585827	10	124,165,615	G	A	0.498	1.03 (1.02-1.05)	8.1x10 ⁻⁸	1.04 (1.02-1.05)	9.5x10 ⁻⁹
<i>TMEM258</i>	rs102275	11	61,557,803	T	C	0.638	1.03 (1.02-1.04)	1.2x10 ⁻⁵	1.03 (1.02-1.04)	1.2x10 ⁻⁵
<i>NRXN3</i>	rs10146997	14	79,945,162	G	A	0.225	1.05 (1.03-1.06)	1.8x10 ⁻¹⁰	1.03 (1.01-1.04)	0.00020
<i>PTPN9</i>	rs4886707	15	75,755,467	C	T	0.718	1.04 (1.02-1.05)	3.8x10 ⁻⁸	1.04 (1.03-1.05)	4.3x10 ⁻⁹
<i>NFAT5</i>	rs1364063	16	69,588,572	T	C	0.621	1.03 (1.01-1.04)	2.3x10 ⁻⁵	1.02 (1.01-1.03)	0.00094
<i>CMIP1</i>	rs2925979	16	81,534,790	T	C	0.305	1.04 (1.02-1.05)	2.5x10 ⁻⁸	1.03 (1.02-1.05)	1.0x10 ⁻⁵
<i>HORMAD2</i>	rs2412980	22	30,592,069	C	T	0.926	1.08 (1.06-1.11)	2.6x10 ⁻¹¹	1.09 (1.06-1.11)	2.8x10 ⁻¹¹

(b) European-specific meta-analysis of 45,927 cases and 248,489 controls.

Locus	Lead SNP	Chr	Position	Alleles		RAF	BMI unadjusted		BMI adjusted	
				Risk	Other		OR (95% CI)	p-value	OR (95% CI)	p-value
Loci overlapping with novel coding association signals										
POC5-ANKDD1B	rs40060	5	74,967,386	T	C	0.642	1.05 (1.03-1.07)	2.8x10 ⁻¹¹	1.03 (1.01-1.04)	7.8x10 ⁻⁵
LPL	rs17482753	8	19,832,646	G	T	0.902	1.05 (1.03-1.07)	1.1x10 ⁻⁵	1.09 (1.07-1.11)	8.0x10 ⁻⁶
C17orf58-BPTF	rs12602912	17	65,870,073	T	C	0.207	1.05 (1.03-1.07)	1.1x10 ⁻⁸	1.03 (1.01-1.05)	0.00011
Loci not overlapping with novel coding association signals										
MRAS	rs2306374	3	138,119,952	C	T	0.164	1.09 (1.08-1.11)	4.3x10 ⁻⁷	1.09 (1.08-1.11)	2.8x10 ⁻⁹
FAM13A	rs13133548	4	89,740,128	A	G	0.471	1.06 (1.05-1.08)	3.6x10 ⁻⁶	1.05 (1.04-1.07)	4.8x10 ⁻⁸
VEGFA	rs6905288	6	43,758,873	A	G	0.563	1.03 (1.01-1.04)	3.2x10 ⁻⁵	1.04 (1.02-1.06)	3.0x10 ⁻⁸
TFAP2B	rs2206277	6	50,798,526	T	C	0.188	1.03 (1.02-1.05)	7.1x10 ⁻⁶	1.04 (1.02-1.05)	0.228
ABO	rs505922	9	136,149,229	C	T	0.362	1.04 (1.02-1.05)	2.7x10 ⁻⁶	1.04 (1.03-1.06)	8.4x10 ⁻⁶

<i>PLEKHA1</i>	rs6585827	10	124,165,615	G	A	0.501	1.05 (1.04-1.07)	1.8x10 ⁻⁶	1.06 (1.05-1.07)	2.0x10 ⁻⁸
<i>TMEM258</i>	rs102275	11	61,557,803	T	C	0.645	1.04 (1.02-1.05)	1.1x10 ⁻⁶	1.04 (1.02-1.06)	5.0x10 ⁻⁸
<i>NRXN3</i>	rs10146997	14	79,945,162	G	A	0.222	1.05 (1.03-1.07)	5.3x10 ⁻¹⁰	1.03 (1.01-1.04)	0.00067
<i>PTPN9</i>	rs4886707	15	75,755,467	C	T	0.761	1.04 (1.02-1.06)	1.5x10 ⁻⁶	1.04 (1.02-1.05)	1.2x10 ⁻⁶
<i>NFAT5</i>	rs1364063	16	69,588,572	T	C	0.579	1.04 (1.03-1.06)	2.5x10 ⁻⁸	1.02 (1.01-1.04)	0.00018
<i>CMIP1</i>	rs2925979	16	81,534,790	T	C	0.304	1.04 (1.02-1.05)	2.1x10 ⁻⁵	1.04 (1.02-1.05)	7.7x10 ⁻⁶
<i>HORMAD2</i>	rs2412980	22	30,592,069	C	T	0.917	1.09 (1.06-1.12)	4.2x10 ⁻⁹	1.09 (1.06-1.11)	4.2x10 ⁻¹⁰

Chr: chromosome. RAF: risk allele frequency. BMI: body mass index. OR: odds ratio. CI: confidence interval.

Supplementary Table 8 | Summary of gene-based signals at *FAM63A* and *PAM*, including single-variant *p*-values.

Gene-based analysis (58,425 cases and 188,032 controls)									Variants included in the masks							
Gene	Mask	Trans-ethnic (58,425 cases and 188,032 controls)			European (41,066 cases and 136,024 controls)			rs ID	Chr	Position	Variant annotation	Trans-ethnic		European		
		Number of variants in the mask	P_{burden}	P_{SKAT}	Number of variants in the mask	P_{burden}	P_{SKAT}					MAF (%)	P	MAF (%)	P	
FAM63	Strict	8	6.2×10^{-7}	9.7×10^{-9}	8	4.1×10^{-7}	4.0×10^{-9}	rs146551660	1	150970119	p.Thr295Met	0.062	0.079	0.039	0.00042	
	Broad	10	2.1×10^{-7}	8.5×10^{-9}	10	4.6×10^{-8}	3.1×10^{-9}	1:150970216	1	150970216	p.Arg263*	0.0085	0.80	0.0050	0.25	
								rs143579361	1	150970680	p.His209Tyr	0.13	0.18	0.15	0.17	
								rs139059568	1	150971879	p.Arg174Gln	0.028	0.12	0.032	0.13	
								rs150431391	1	150971880	p.Arg174*	0.014	0.29	0.018	0.24	
								rs138246511	1	150971949	p.Gln151*	0.0082	0.47	0.023	0.34	
								rs140386498	1	150972959	p.Tyr95Asn	1.1	2×10^{-8}	1.4	1×10^{-8}	
								rs145467872	1	150973013	p.Asp77Asn	0.15	0.65	0.16	0.63	
								rs142215084	1	150974740	p.Trp166*	0.074	0.98	0.077	0.88	
							rs138505497	1	150974828	p.Glu137Gly	0.062	0.85	0.020	0.18		
PAM	Strict	7	2.6×10^{-8}	1.1×10^{-8}	7	4.3×10^{-8}	2.7×10^{-8}	rs199856250	5	102201978	p.Val27Ile	0.0077	0.54	0.011	0.17	
	Broad	17	1.4×10^{-7}	8.2×10^{-9}	15	3.0×10^{-7}	1.5×10^{-8}	rs200066052	5	102203047	p.Ser54Pro	0.029	0.91	0.030	0.90	
								rs201199380	5	102203059	p.Ala58Thr	0.034	0.81	0.035	0.72	
								rs181340861	5	102260735	p.Arg144Gln	0.056	0.73	0.019	0.90	
								rs145099851	5	102282583	p.Arg190His	0.10	0.28	0.12	0.17	
								rs201009674	5	102285612	p.Val244Ala	0.062	0.88	0.071	0.82	
								rs147370276	5	102295628	p.Glu319Gln	0.0090	0.97	0.009	0.97	
								rs61729214	5	102295724	p.Val351Met	0.041	0.52	0.012	0.65	
								rs139660283	5	102309859	p.Arg401Lys	0.015	0.92	0.011	0.75	
								rs145710876	5	102310011	p.Ile452Val	0.059	0.35	0.00	-	
								rs144310649	5	102310060	p.Leu468Ser	0.027	0.13	0.028	0.60	
								rs114049029	5	102310135	p.Thr493Ile	0.16	0.59	0.00	-	
								rs150469595	5	102338783	p.Ile554Val	0.046	0.73	0.047	0.74	
								rs35658696	5	102338811	p.Asp563Gly	4.0	7×10^{-9}	5.0	3.1×10^{-8}	
								rs186632214	5	102343266	p.Arg707Gln	0.016	0.50	0.0073	0.43	
								rs200646882	5	102345565	p.Arg776Cys	0.014	0.69	0.014	0.38	
								rs137865834	5	102364597	p.Gly918Glu	0.028	0.98	0.027	0.91	

Chr: chromosome. MAF: minor allele frequency. Variants included only in the strict mask are highlighted in grey.

Supplementary Tables 9, 10, and 11 can be found in the Supplementary excel files.

Supplementary Table 9 | Study characteristics and analysis details of studies included in the DIAGRAM consortium GWAS.

Supplementary Table 10 | Summary of fine-mapping analyses with functionally unweighted and annotation informed prior.

Supplementary Table 11 | Association of T2D signals with various metabolic and anthropometric traits.

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1958 Birth Cohort	We are grateful for being able to use the British 1958 Birth Cohort DNA collection. Sample collection funded by the Medical Research Council grant G0000934 and the Wellcome Trust grant 068545/Z/02. Genotyping was funded by the Wellcome Trust.
AGES	This study has been funded by NIH contracts N01-AG-1-2100 and 271201200022C, the NIA Intramural Research Program, Hjartavernd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament). The study is approved by the Icelandic National Bioethics Committee, VSN: 00-063. The researchers are indebted to the participants for their willingness to participate in the study.
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iv. Consortium membership

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